Signifor® (pasireotide) for the Treatment of Cushing's Disease

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 7, 2012

NOVARTIS

Introduction

Germo Gericke, MD

Novartis Pharma

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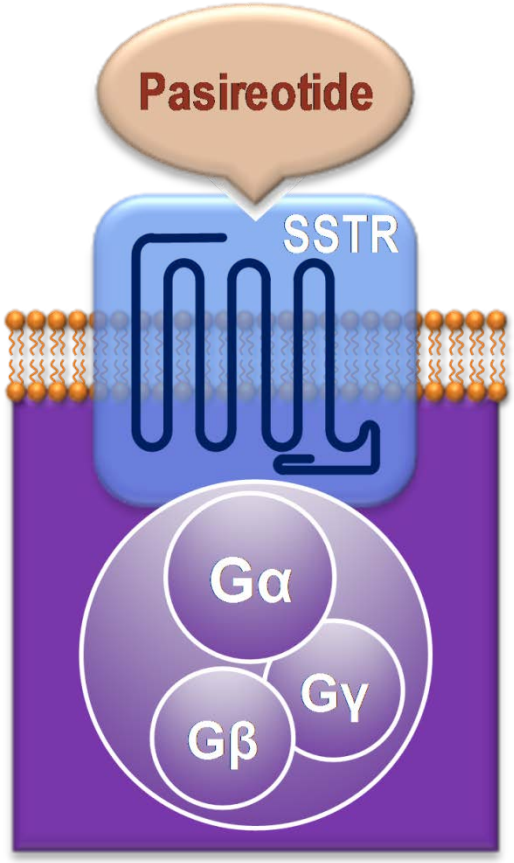
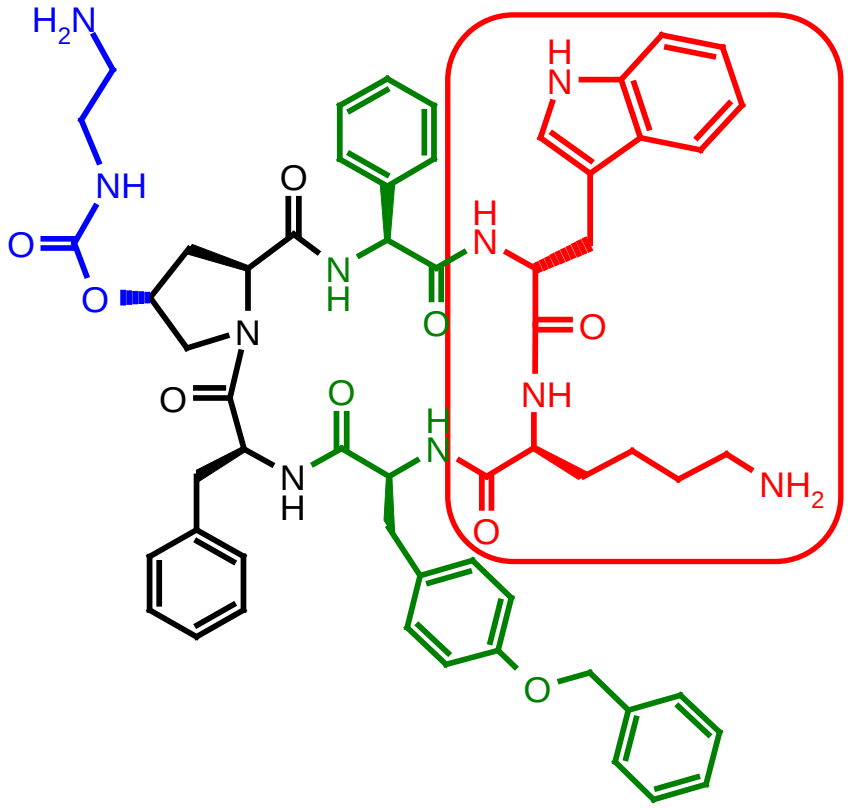
Pasireotide Is a Novel Pituitary-Targeted Therapy for Cushing's Disease

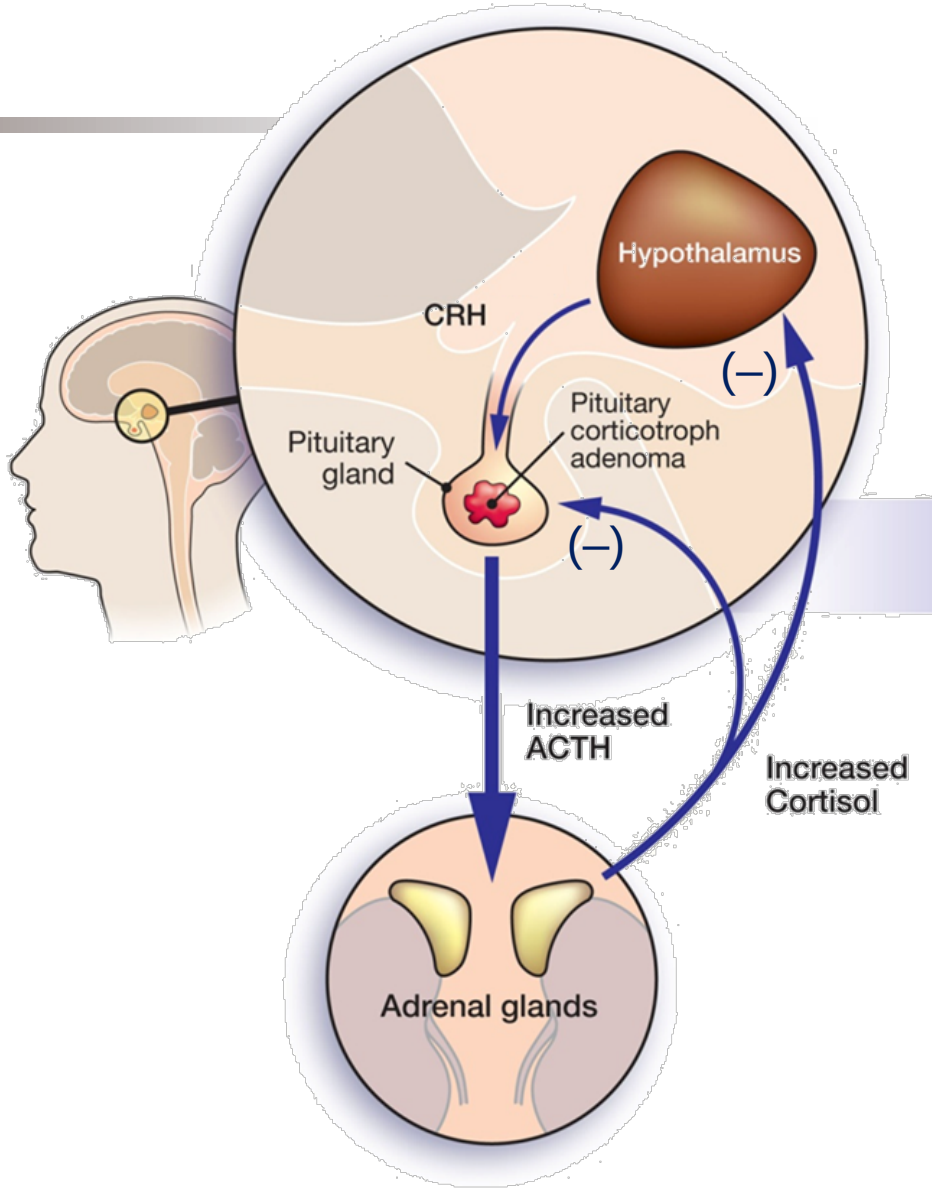
Pasireotide: a 2nd-generation somatostatin analogue





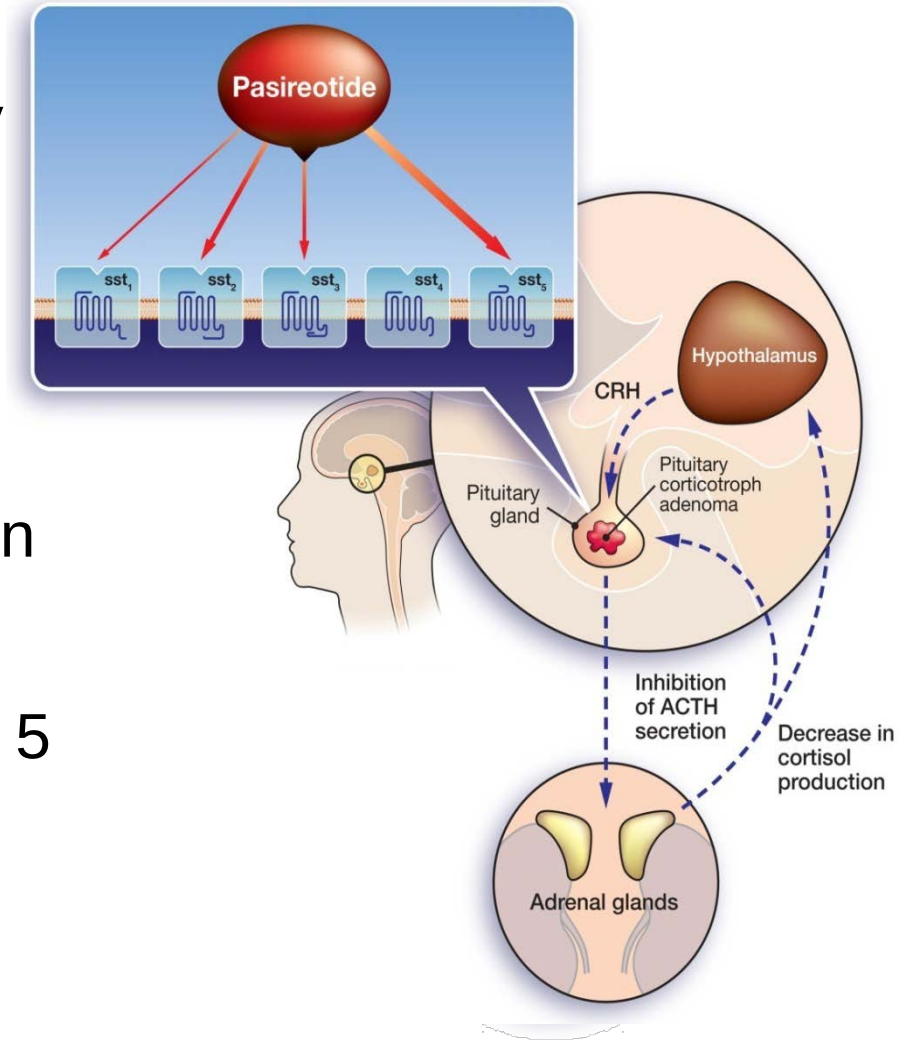
Cushing's Disease

- Rare endocrine disorder with orphan designation
- Driven by pituitary adenoma over-secreting ACTH
- Hypercortisolism results in significant and complex morbidity and mortality
- Unmet medical need despite available therapies



Pasireotide Acts Centrally by Suppressing ACTH Secretion

- Pituitary adenomas causing Cushing's disease frequently over-express somatostatin receptor subtype 5
- Activation of somatostatin receptors reduces hormone secretion and cell proliferation
- Pasireotide demonstrates
  - High affinity to sstr1,2,3 & 5
  - Suppression of ACTH secretion in vitro



Development Program for Pasireotide

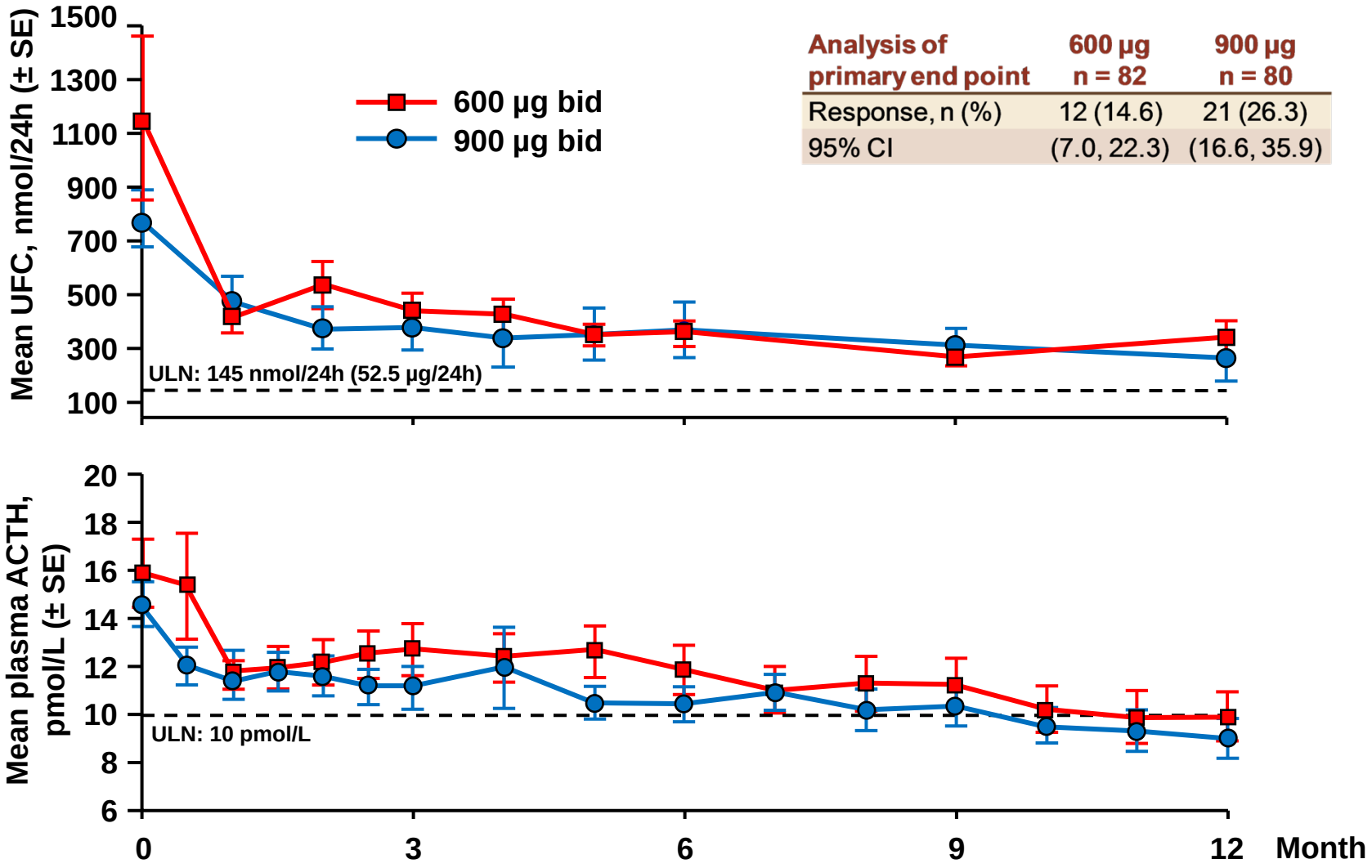
- Comprehensive preclinical program
- Healthy volunteer studies
  - Completed (N = 723): PK and PK/PD, thorough QT, impaired hepatic function, glucose metabolism
  - Ongoing: impaired renal function, drug-drug interaction
- Phase II/III program in multiple indications (sc and LAR formulations)
  - Pituitary diseases: Cushing's and acromegaly
  - Gastroenteropancreatic neuroendocrine (GEP/NET) and other malignant tumors

NDA for Cushing's Disease

- B2305 (N = 162)
  - Largest randomized study in Cushing's disease
  - Design agreements with FDA
    - 2-dose randomized study (independent cohorts)
    - Primary endpoint: normal UFC at Month 6 and 15% lower bound of confidence interval
- B2208 (N = 39)
  - Phase II (rationale for dose selection)
- Ongoing extensions for both studies
- Additional safety information from development program

Pasireotide Reduces UFC and ACTH Levels

Study B2305



Analysis of primary end point	600 µg n = 82	900 µg n = 80
Response, n (%)	12 (14.6)	21 (26.3)
95% CI	(7.0, 22.3)	(16.6, 35.9)

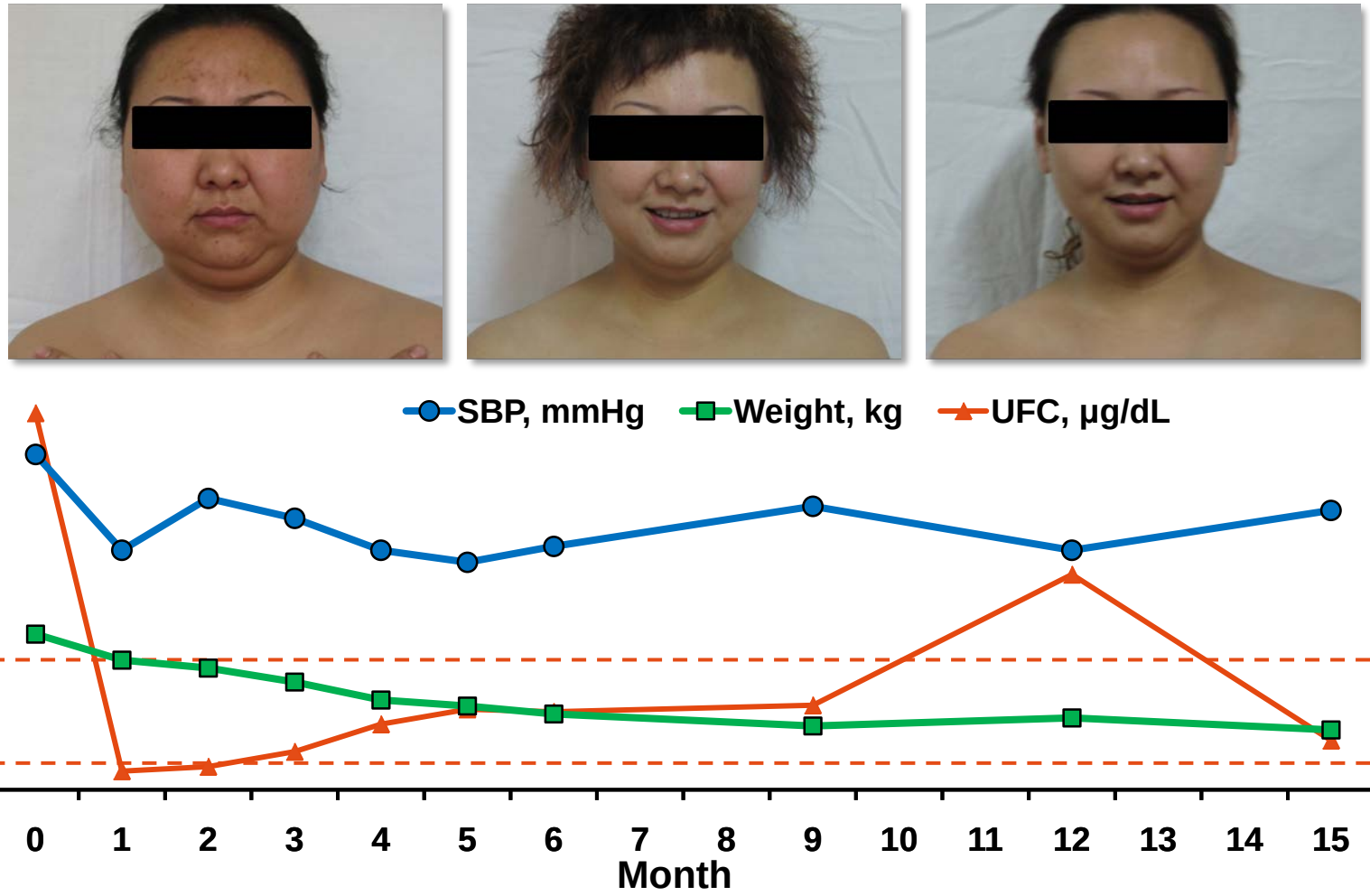
Pasireotide Improves Morbidity Related to Cushing's Disease

Study B2305

- Systolic and diastolic blood pressure
  - Regardless of use of antihypertensive medications
- Lipid levels, particularly LDL-C and triglycerides
- Body weight, BMI, and waist circumference
- Physical features such as facial rubor, striae, and fat pads

Pasireotide Improves Physical Features of Cushing's Disease

Study B2305



Safety Profile and Risk Minimization

- Safety profile similar to 1st-generation analogues
- Hyperglycemia
  - Mechanism well understood: insulin and incretin inhibition; no effect on insulin sensitivity
  - Reversible on treatment discontinuation
- Liver function abnormalities, prolongation of QT interval, and hypocortisolism
  - Addressed by recommendations for monitoring and management in prescribing information
- Proposed risk minimization includes a medication guide and distribution via central pharmacy

Early Individual Assessment Strengthens Positive Benefit:Risk Profile

- Cushing's disease is debilitating with high unmet medical need
- Efficacy and safety of pasireotide have been established and can be monitored effectively; individual profile can be assessed early
- Risk minimization provides adequate guidance to ensure safe and effective use of pasireotide

Proposed Indication:
Treatment of patients with Cushing's disease who require medical therapeutic intervention

Pasireotide Presentation Overview

Introduction	**Germo Gericke, MD** Novartis Pharma
Cushing's Disease – Unmet Need	**Maria Fleseriu, MD, FACE** Oregon Health & Science University
Efficacy Profile of Pasireotide Safety and Risk Minimization	**Pablo Cagnoni, MD** Novartis Pharma
Hyperglycemia Mechanism and Management	**Sonia Caprio, MD** Yale University
Clinical Perspective on the Treatment of Cushing's Disease	**Shlomo Melmed, MB, ChB, MACP** Cedars-Sinai Medical Center

Consultants

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Cushing's Disease—Unmet Need

Maria Fleseriu, MD, FACE

Associate Professor Medicine/Endocrinology and Neurological Surgery
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Oregon Health & Science University

Disclosure Statement

- Scientific consultant fees from Novartis Pharmaceuticals and Ipsen
- Principal Investigator in Cushing's clinical trials sponsored by Novartis Pharmaceuticals and Corcept Therapeutics, with research support to OHSU
- Principal Investigator in acromegaly clinical trials sponsored by Ipsen and Novartis, with research support to OHSU

Cushing's Disease

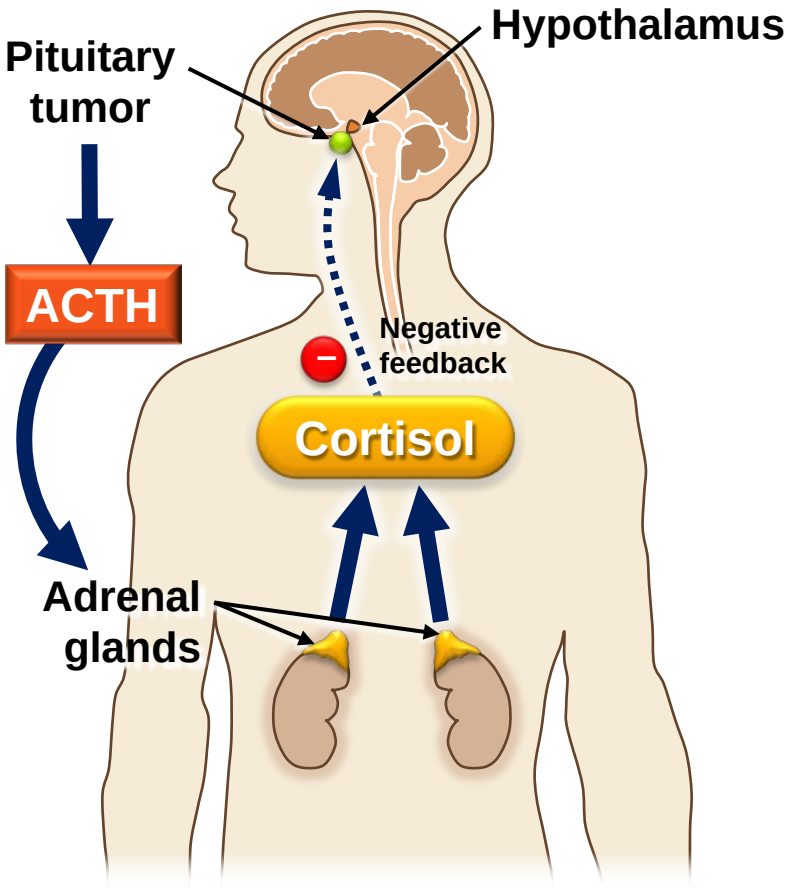
Introduction

Cushing's Syndrome (CS)

- Signs, symptoms and comorbidities from prolonged exposure to excess endogenous or exogenous glucocorticoids

Cushing's Disease

- Most common cause of CS
- Due to an adrenocorticotropin (ACTH)-secreting pituitary adenoma
  - Stimulates adrenal cortisol overproduction



Etxabe J & Vazquez JA. *Clin Endocrinol (Oxf).* 1994;40(4):479-484.
Nieman LK & Ilias I. *Am J Med.* 2005;118(12):1340-1346.

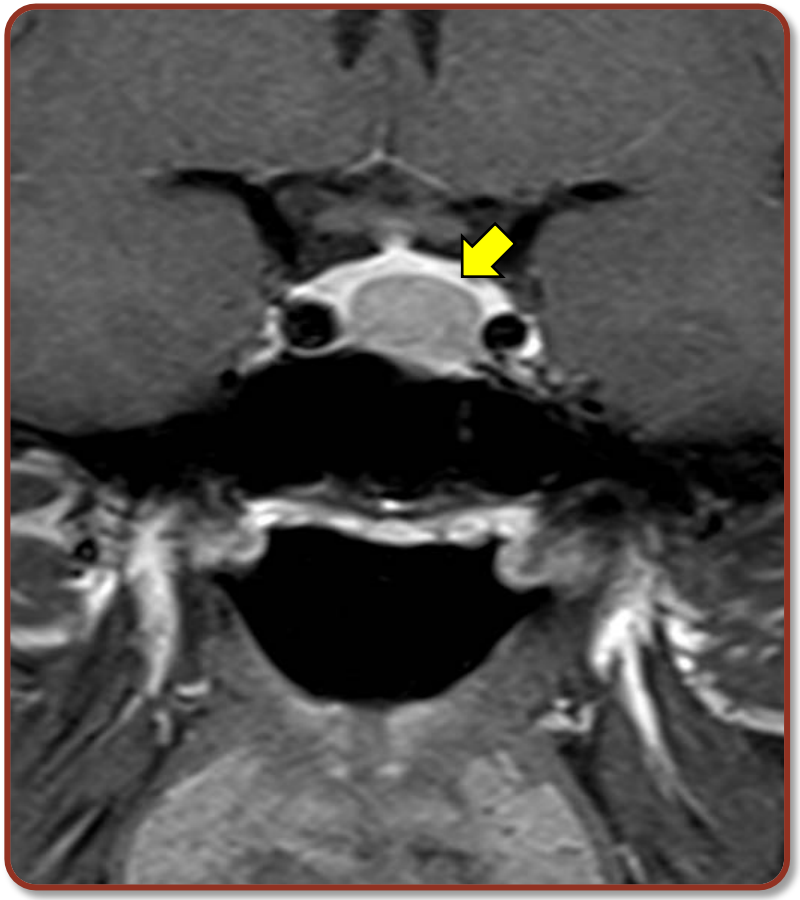
Cushing's Disease Epidemiology

- Rare condition
- Estimated US prevalence ~17,000[a]
  Higher in European reports[b,c,d,e,f]
- Female predominant (3.5-fold more than men[g])
  - No gender difference in tumor pathophysiology
- Median age at diagnosis 41.1 years
  (range, 7.6 - 69.7 years)[d]

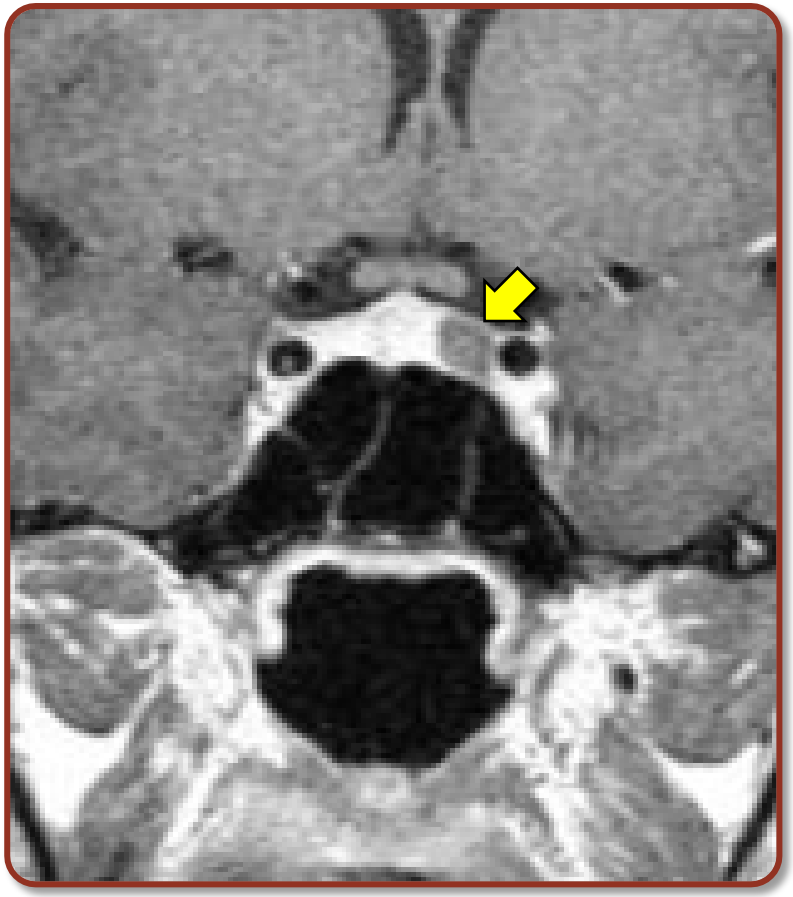
[a] Based on information provided in Daly AF, et al. *J Clin Endocrinol Metab*. 2006;91(12):4769-4775.
[b] Etxabe J & Vazquez JA. *Clin Endocrinol (Oxf)* .1994;40(4):479-484.
[c] Ambrosi B, et al. *Excerpta Medica*. 1991;159-168.
[d] Lindholm J, et al. *J Clin Endocrinol Metab*. 2001;86(1):117-123.
[e] Daly AF, et al. *J Clin Endocrinol Metab*. 2006;91(12):4769-4775.
[f] Fernandez. *Clin Endocrinol*. 2010;72:377.
[g] Newell-Price J, et al. *Lancet*. 2006;367(9522):1605-1617.

MRI of Cushing Macroadenoma and Microadenoma

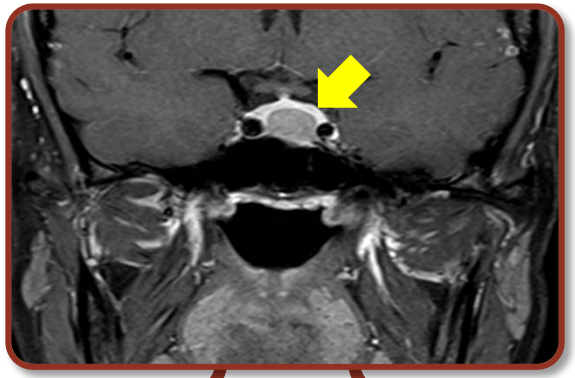
Macroadenoma



Microadenoma



Pathogenesis of Cushing's Disease



Hormone hypersecretion

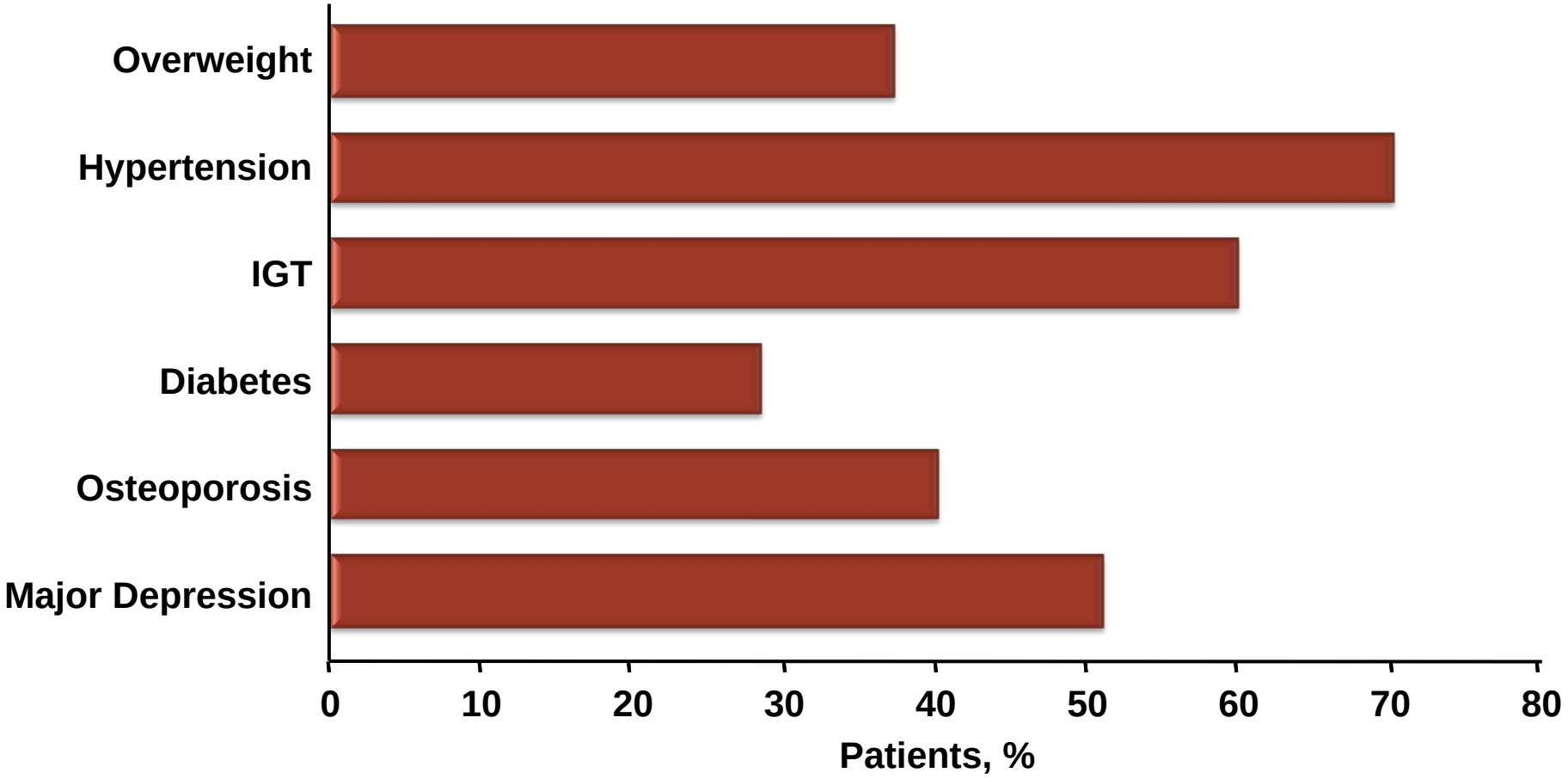
- ⬆ ACTH → ⬆ cortisol → ⬆ UFC
  - Moon face
  - Central fat deposits
  - Ecchymosis
  - Hirsutism
  - Acne
  - Muscle weakness
  - Infections

Central mass effects

- Pituitary hormone deficiencies
- Visual field disturbance
- Headache
- Parasellar invasion

Adapted from Melmed S. *J Clin Invest.* 2003;112(11):1603-1618.

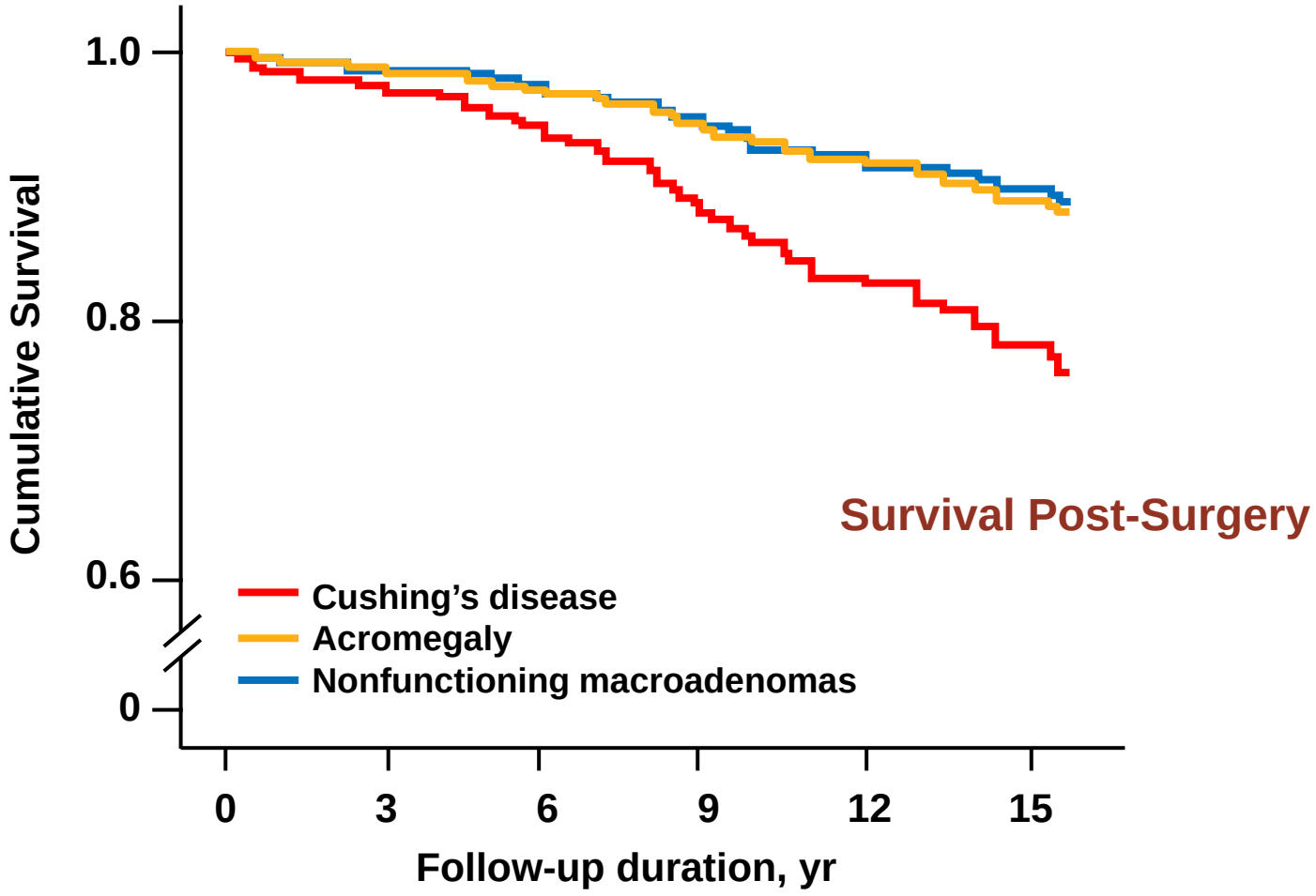
Comorbidities in Cushing's Disease



IGT = impaired glucose tolerance.

Feelders RA, et al. *Eur J Endocrinol*. 2012;167(3):311-326.

Mortality in Cushing's Disease



Dekkers OM, et al. *J Clin Endocrinol Metab*. 2007;92(3):976-981.

Approaches in the Treatment of Patients With Cushing's Disease

- Pituitary surgery
- Pituitary radiation
- Bilateral adrenalectomy
- Medical therapy

Tritos NA, et al. *Nat Rev Endocrinol*. 2011;7(5):279-289; van der Pas R, et al. *Endocr Relat Cancer*. 2012 Aug 30. [Epub ahead of print]; Fleseriu M. *Neurosurg Clin N Am*. 2012;23(4):653-668; Fleseriu M & Petersenn S. *Pituitary*. 2012;15(3):330-341.

Cushing's Disease Surgery: First-Line

Advantages

- Rapid initial remission[a]
  - Micro: 65% - 90%
  - Macro: < 65%
- Potential cure
- One-time cost

Disadvantages

- Not all patients appropriate candidates due to comorbidities, frailty; some refuse
- Tumor and ACTH hypersecretion could persist or recur

Determinants of success:

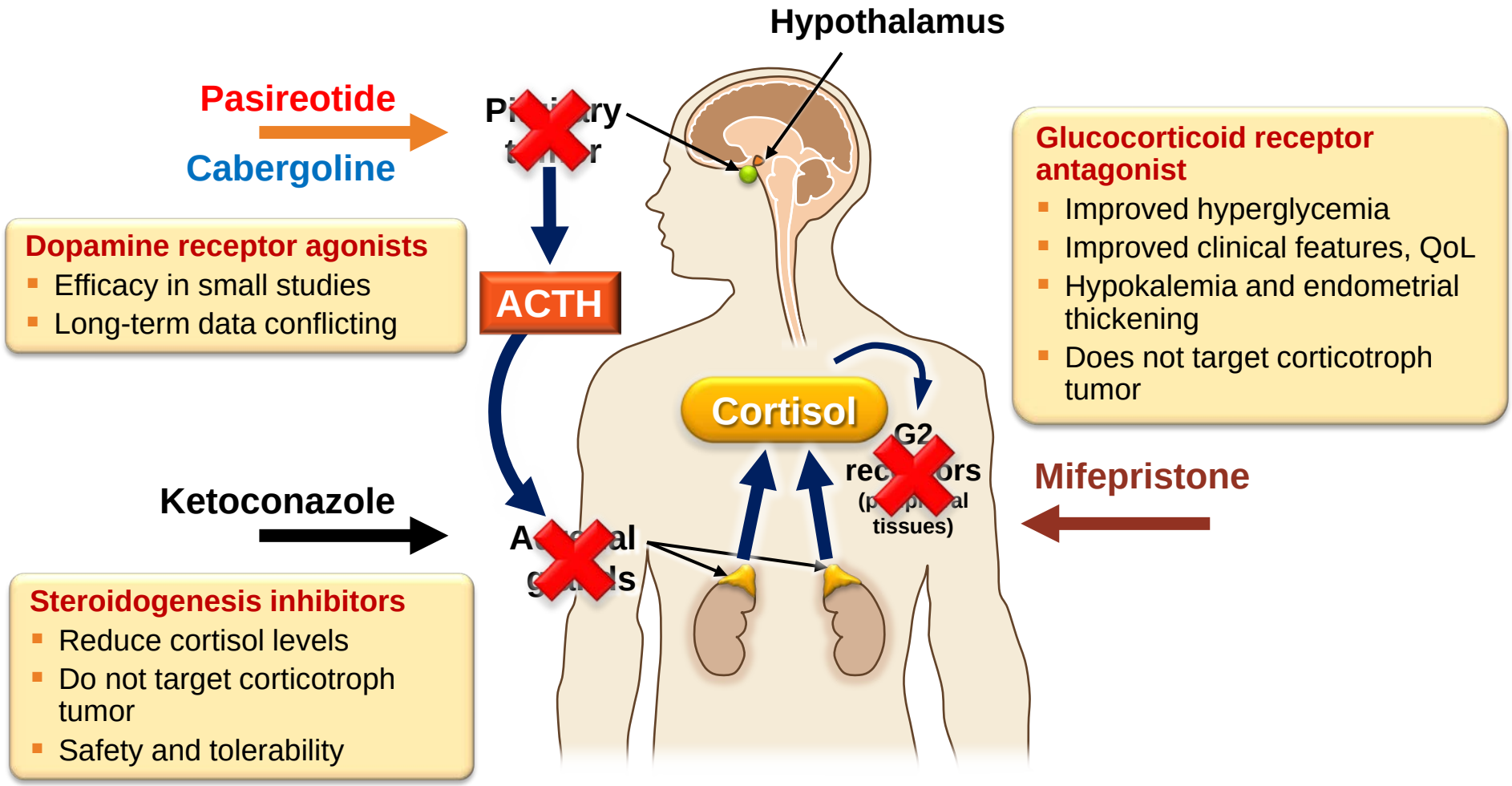
- High-volume surgeon
- Tumor visibility

[a] **Biller BMK, et al. *J Clin Endocrinol Metab*. 2008;93(7):2454-2462.**

Individualized Second-Line Treatment

- More radical pituitary surgery
  - **Pro:** Potential for cure
  - **Con:** Lower cure rate, higher complication rates and increased risk of hypopituitarism, especially for repeat surgery
- Radiation therapy
  - **Pro:** Potential for cure
  - **Con:** Delayed efficacy for years, hypopituitarism/local CNS damage, increased mortality with conventional radiation
- Bilateral adrenalectomy
  - **Pro:** Immediate hypercortisolism reversal
  - **Con:** Life-long glucocorticoid and mineralocorticoid replacement, risk of adrenal crisis and of Nelson's syndrome (corticotroph tumor progression)

Medical Treatment Options



Dopamine receptor agonists
- Efficacy in small studies
- Long-term data conflicting

Steroidogenesis inhibitors
- Reduce cortisol levels
- Do not target corticotroph tumor
- Safety and tolerability

Glucocorticoid receptor antagonist
- Improved hyperglycemia
- Improved clinical features, QoL
- Hypokalemia and endometrial thickening
- Does not target corticotroph tumor

Cushing's Disease—Treatment Goals

- Expert Consensus Statement of the Pituitary Society and the European Neuroendocrine Association[a]
  - Normalization of biochemical changes (UFC, ACTH) with minimal morbidity
  - Reversal of clinical features
  - Long-term control without recurrence

[a] **Biller BMK, et al. *J Clin Endocrinol Metab*. 2008;93(7):2454-2462.**

Cushing's Disease—Unmet Need Conclusions

- High morbidity and mortality
- Surgery is the first-line treatment of choice
- ~ 50% require additional treatment
- Second-line medical options pose unique challenges
- Unmet need for a well-studied drug that addresses the underlying cause of the disease
  - Pituitary-directed therapies provide new hope
  - Have the potential to provide meaningful reductions in ACTH levels and tumor volume

Pasireotide in the Treatment of Patients With Cushing's Disease

Pablo Cagnoni, MD

Novartis Pharma

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Presentation Overview

- Clinical Pharmacology
- Study Design and Efficacy Results
  - Phase II Study B2208
  - Phase III Study B2305
- Efficacy Conclusions

Pasireotide Clinical Pharmacology Summary

- Rapid absorption, extensive distribution, minimal metabolism, low clearance
  - Hepatic clearance as main elimination pathway; renal clearance minimal
- Effective half-life ~12 hours supports bid dosing regimen
- Low potential for drug-drug interaction

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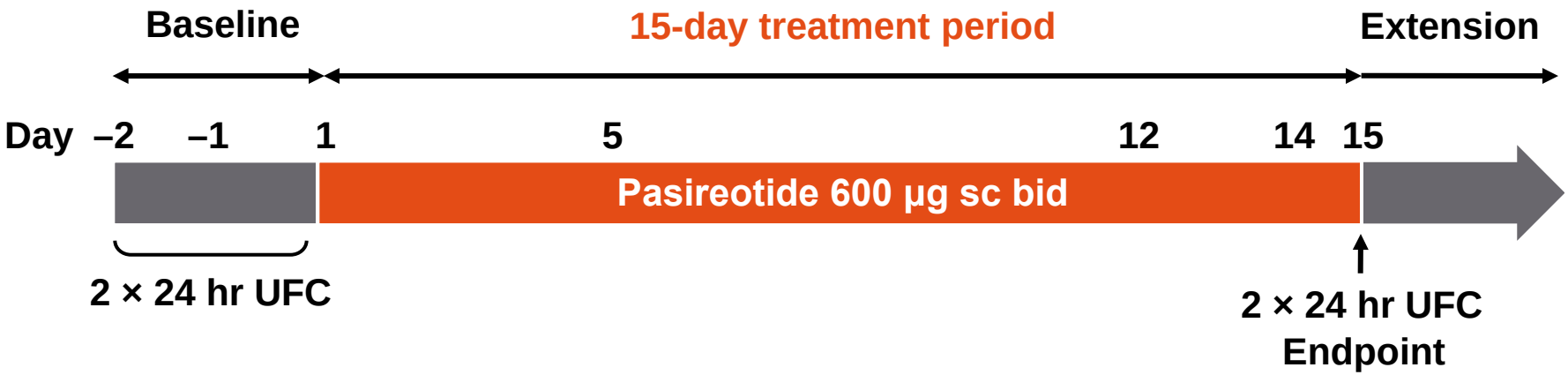
Pasireotide Phase II Trial In Cushing's Disease
Study B2208

- Proof-of-concept, open-label, single-arm, multicenter
- Designed to assess short-term efficacy, safety, and PK



- Patients who derived clinical benefit eligible for extension
  - Up- or down-titration of dose was allowed

Boscaro M, et al. *J Clin Endocrinol Metab*. 2009;94(1):115-122.

Pasireotide Phase II Trial Results

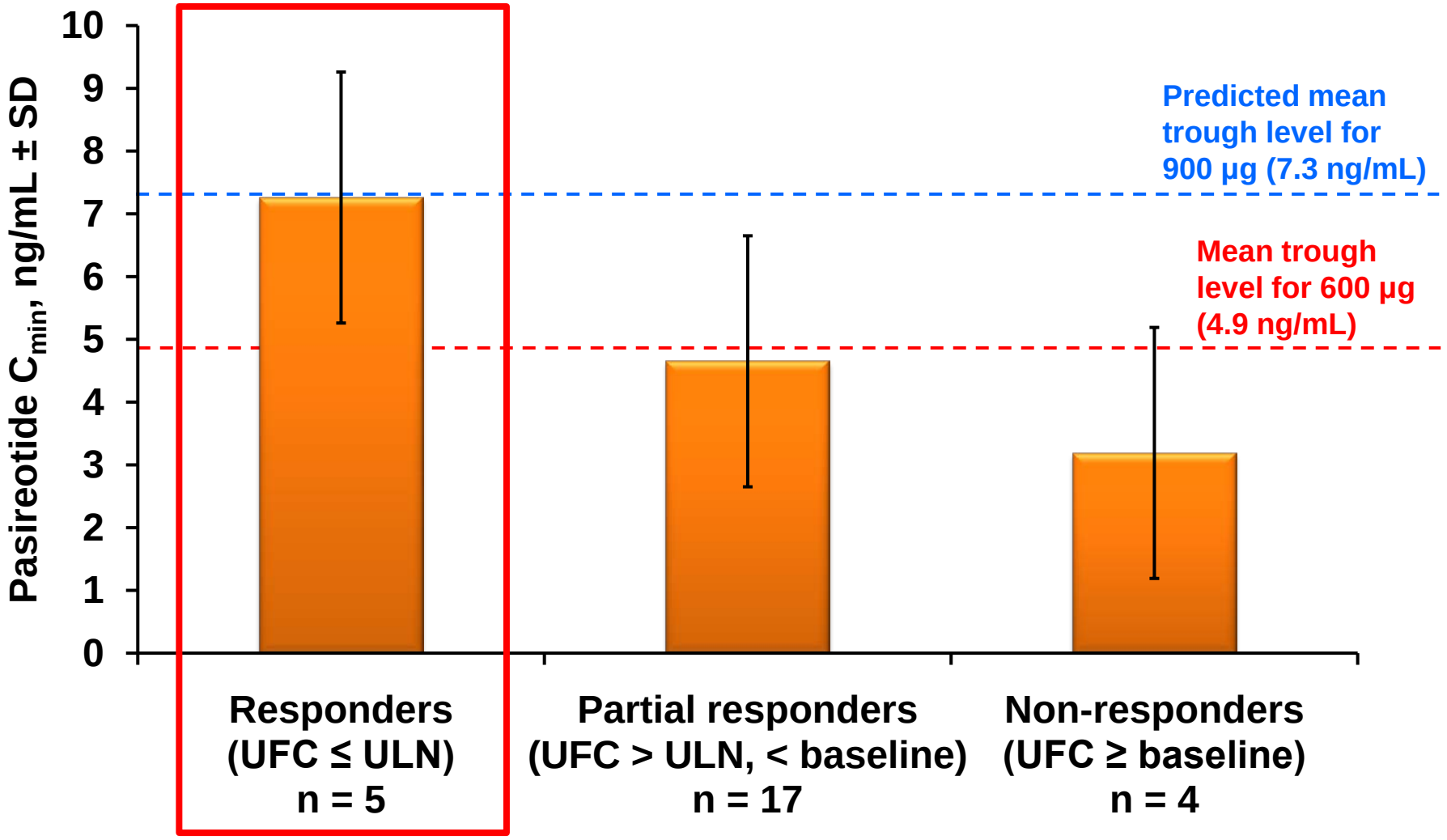
Study B2208

	Day 15[a]	Month 6
UFC levels normalized (ULN = 100 µg/24 hr)	17% (5/29)	22% (4/18)
Mean UFC decrease	446 to 248 µg/24 hr	442 to 153 µg/24 hr
UFC levels decreased	76% (22/29)	56% (10/18)

[a] **Boscaro M, et al. *J Clin Endocrinol Metab*. 2009;94(1):115-122.**

Exposure/Response Analysis Supports Phase 3 Dose Selection

Study B2208



Presentation Overview

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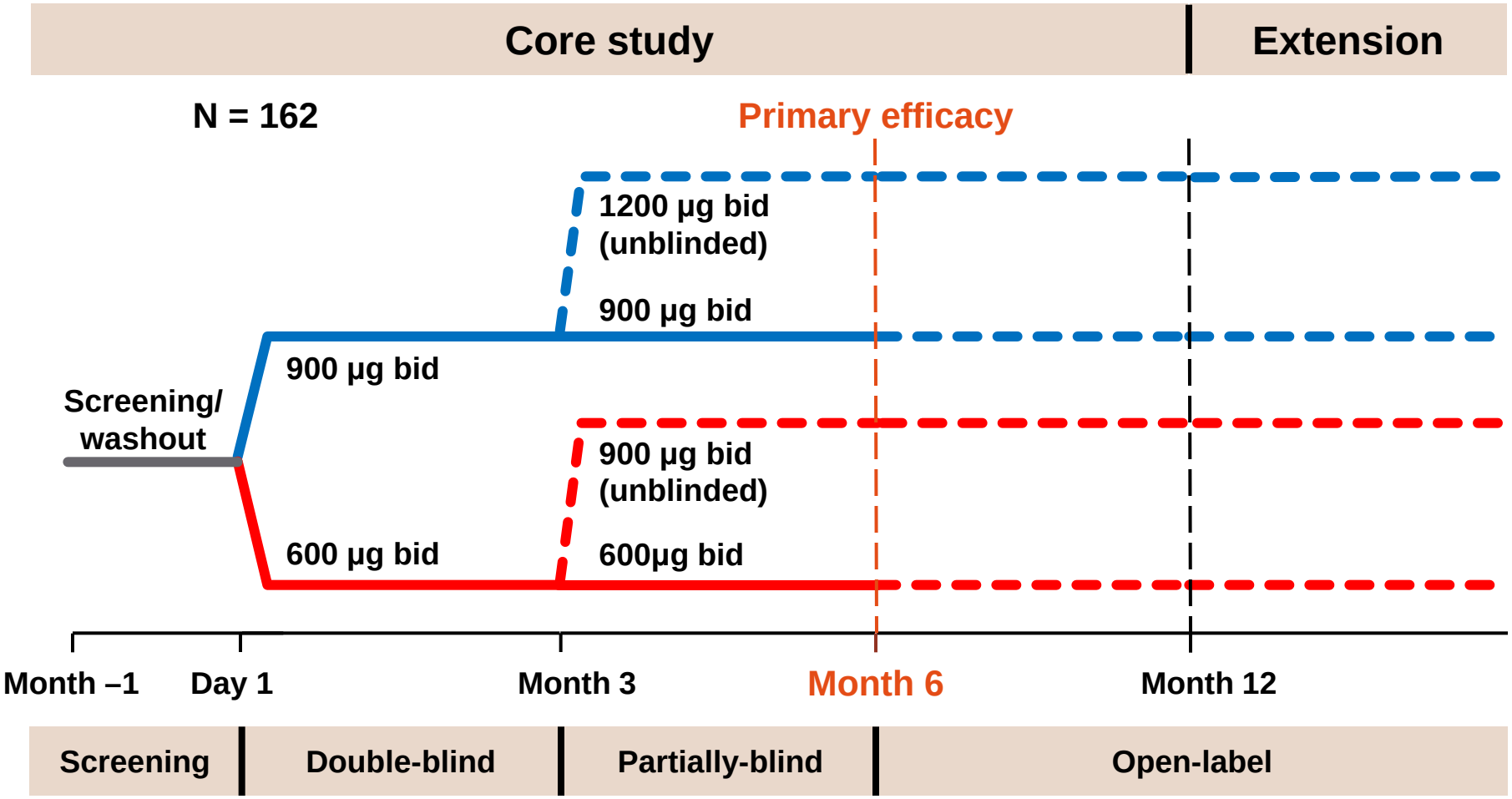
- Efficacy Conclusions

Study Design
Study B2305

- Largest multicenter, randomized, blinded study in Cushing's disease
  - 68 sites across 18 countries
  - 162 patients randomized (Dec 2006 to Mar 2009)
  - Last patient 12-month visit: Mar 2010
  - 90-day update includes data with a 33 months cutoff
- Study objective
  - Evaluate the safety and efficacy of 2 different doses of pasireotide in patients with untreated or recurrent/persistent Cushing's disease

Study Design

Study B2305



Efficacy Endpoints
Study B2305

- Primary (month 6)
  - % of patients with UFC ≤ ULN
    (patients uptitrated prior to month 6 considered non-responders)
- Supportive (month 6)
  - % of patients with UFC ≤ ULN regardless of up-titration
  - Partial responders UFC > ULN with ≥ 50% reduction from baseline
- Secondary (over time)
  - % of patients with UFC ≤ ULN
  - Changes in plasma ACTH, UFC, serum cortisol
  - Changes in clinical signs of hypercortisolism
  - CushingQoL questionnaire

UFC = Mean UFC of ≥ 3 (24 hour) urine samples per patient.

UFC: Month 6 Response Subgroups

Study B2305

- Controlled:
  - Month 6 UFC ≤ ULN regardless of dose-titration
- Partially controlled:
  - Month 6 UFC > ULN, but decreased ≥ 50% from baseline
- Uncontrolled:
  - Month 6 UFC > ULN, and decreased < 50% from baseline
  - Missing values

Statistical Considerations for the Primary Efficacy Endpoint

Study B2305

- Primary Endpoint at Month 6
  - % of randomized and treated patients with UFC ≤ ULN
    - Missing Month 6 UFC imputed by the latest UFC (≥ 3 samples) between Month 3 and 6
    - Several sensitivity analyses for other missing data
- Sample size
  - Null hypothesis of 15% and alternative hypothesis of 30%
  - 73 patients in each group provided 87% power to demonstrate statistical significance at 5% 2-sided level
  - Study not designed to compare the 2 groups
- Dose considered effective if lower bound of the 95% CI > 15%

UFC = Mean UFC of ≥ 3 (24 hour) urine samples per patient.

Selection of 15% Response Rate as Lower Bound of 95% CI

- Cushing's disease has a very low spontaneous cure rate[a]
- Considered clinically meaningful in this setting
- 15% minimal response rate was endorsed by
  - External Cushing's disease Advisory Board
  - Study B2305 Steering Committee
  - FDA

[a] Taylor HC, et al. *Endocr Pract.* 2003;9(2):147-51.

Key Inclusion and Exclusion Criteria
Study B2305

Key inclusion criteria

- Adult patients with confirmed diagnosis of Cushing's disease (baseline UFC ≥ 1.5 × ULN)
- Untreated Cushing's disease if not candidates for pituitary surgery
  - Poor surgical candidates, surgically unapproachable tumors, refuse surgery
- Adequate washout of prior medical therapy

Key exclusion criteria

- Pituitary irradiation within the last 10 years
- Poorly controlled diabetes mellitus (HbA1C > 8%)
- Risk factors for QTc prolongation and torsade de pointes
- Significant liver disease or with ALT/AST > 2 × ULN or TB > 2 × ULN

Rigorous Trial Conduct

Study B2305

- All laboratory assessments conducted in central laboratory
- Rigorous criteria for confirmation of Cushing's disease
- Quadruple UFC 24-hour urine samples at baseline, and 3, 6, and 12 months
- Central independent review of radiologic assessments of tumor volume
- Blinded independent review of physical features of Cushing's disease

Baseline Characteristics

Study B2305

	600 µg n = 82	900 µg n = 80
Mean age, years	40.5	39.9
Female, n (%)	62 (75.6)	64 (80.0)
Cushing's disease status, n (%)		
De novo	15 (18.3)	12 (15.0)
Persistent/recurrent	67 (81.7)	68 (85.0)
Previous therapy, n (%)		
Pituitary surgery	64 (78.0)	64 (80.0)
Pituitary irradiation	3 (3.7)	4 (5.0)
Medication	36 (43.9)	42 (52.5)
UFC, nmol/24 h		
Mean (SD)	1155.9 (2629.8)	781.9 (926.4)
Median (range)	730.0 (219.5-22943.8)	487.0 (195.0-6122.8)

Patient Disposition

Study B2305

	Patients, n (%)	
	600 µg n = 82	900 µg n = 80
Completed		
6 months	54 (65.9)	53 (66.3)
12 months	39 (47.6)	39 (48.8)
Reason for discontinuation (at any time)		
Unsatisfactory therapeutic effect	19 (23.2)	22 (27.5)
Adverse events	13 (15.9)	15 (18.8)
Subject withdrew consent	13 (15.9)	11 (13.8)
Protocol deviation	4 (4.9)	0

Early discontinuations due to AEs; later discontinuations due to lack of efficacy.

UFC Normalization at Month 6

Study B2305

- 900 µg group met primary endpoint

	600 µg n = 82	900 µg n = 80
Response[a], n (%)	12 (14.6)	21 (26.3)
95% confidence interval[b]	(7.0, 22.3)	(16.6, 35.9)

[a] Responders were defined at Month 6 as patients with mUFC ≤ ULN who did not up-titrate pasireotide prior to Month 6.

[b] Normal approximation.

At 6 Months, 34% to 41% of Patients Were Controlled or Partially Controlled

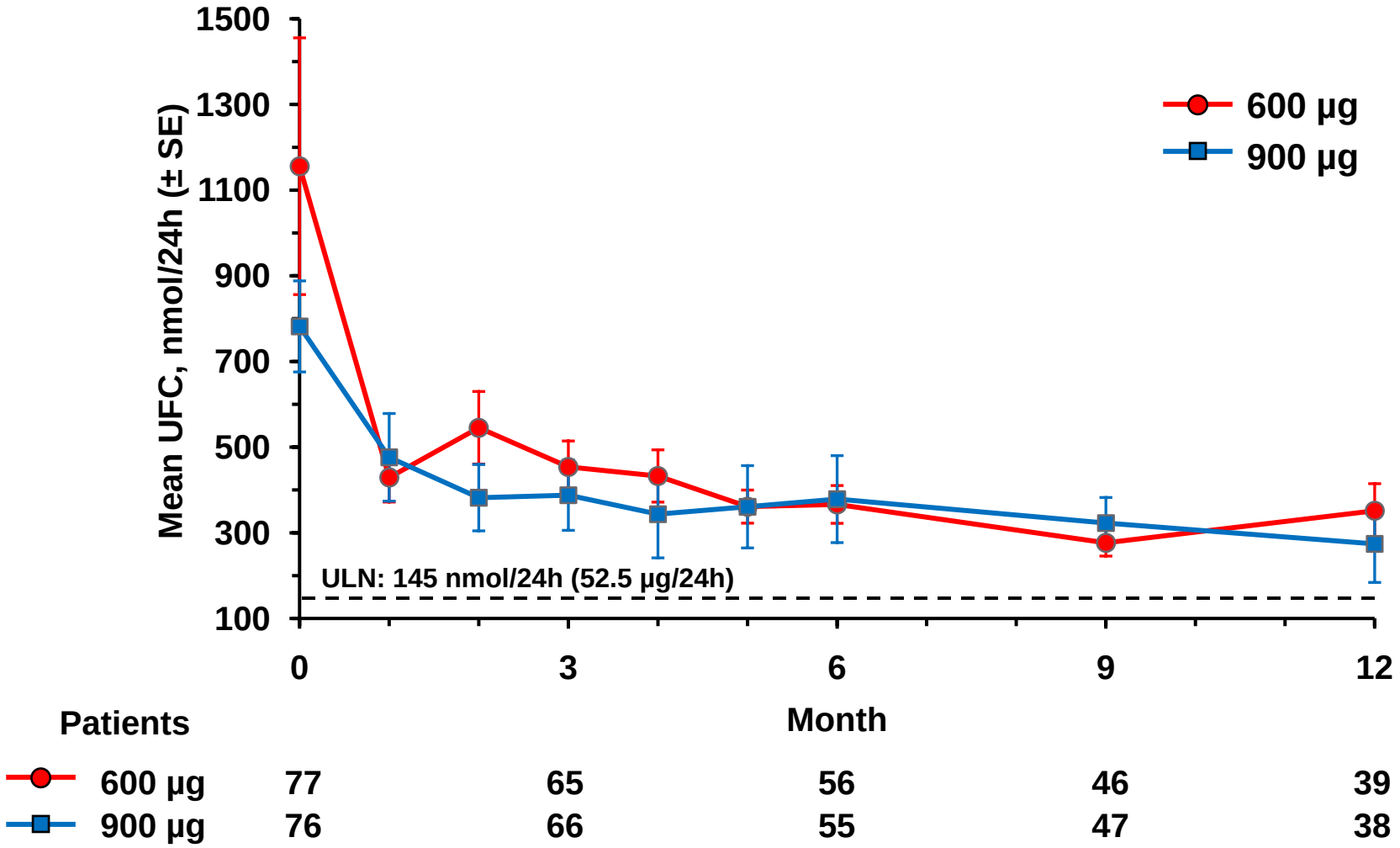
Study B2305

	Patients, n (%)	
	600 µg n = 82	900 µg n = 80
Month 6		
Controlled, n (%)	13 (15.9)	23 (28.8)
Partially Controlled, n (%)	15 (18.3)	10 (12.5)
C + PC, n (%)	28 (34.1)	33 (41.2)
Month 12		
Controlled, n (%)	11 (13.4)	20 (25.0)
Partially Controlled, n (%)	13 (15.9)	2 (2.5)
C + PC, n (%)	24 (29.3)	22 (27.5)

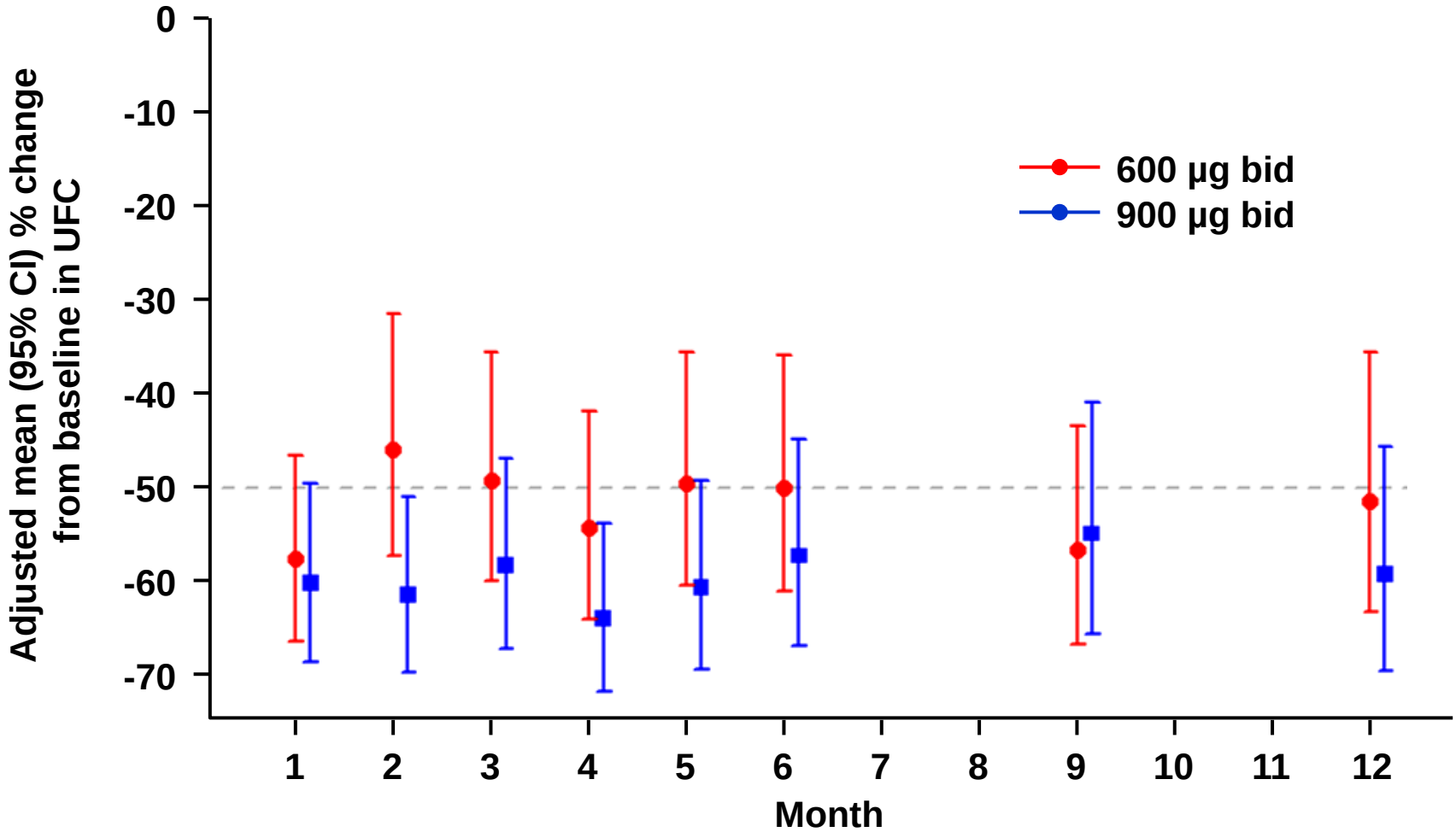
Controlled: UFC ≤ ULN, regardless of dose titration.
Partially Controlled: UFC > ULN, but had ≥ 50% reduction from baseline.

Mean UFC Levels Over Time

Study B2305



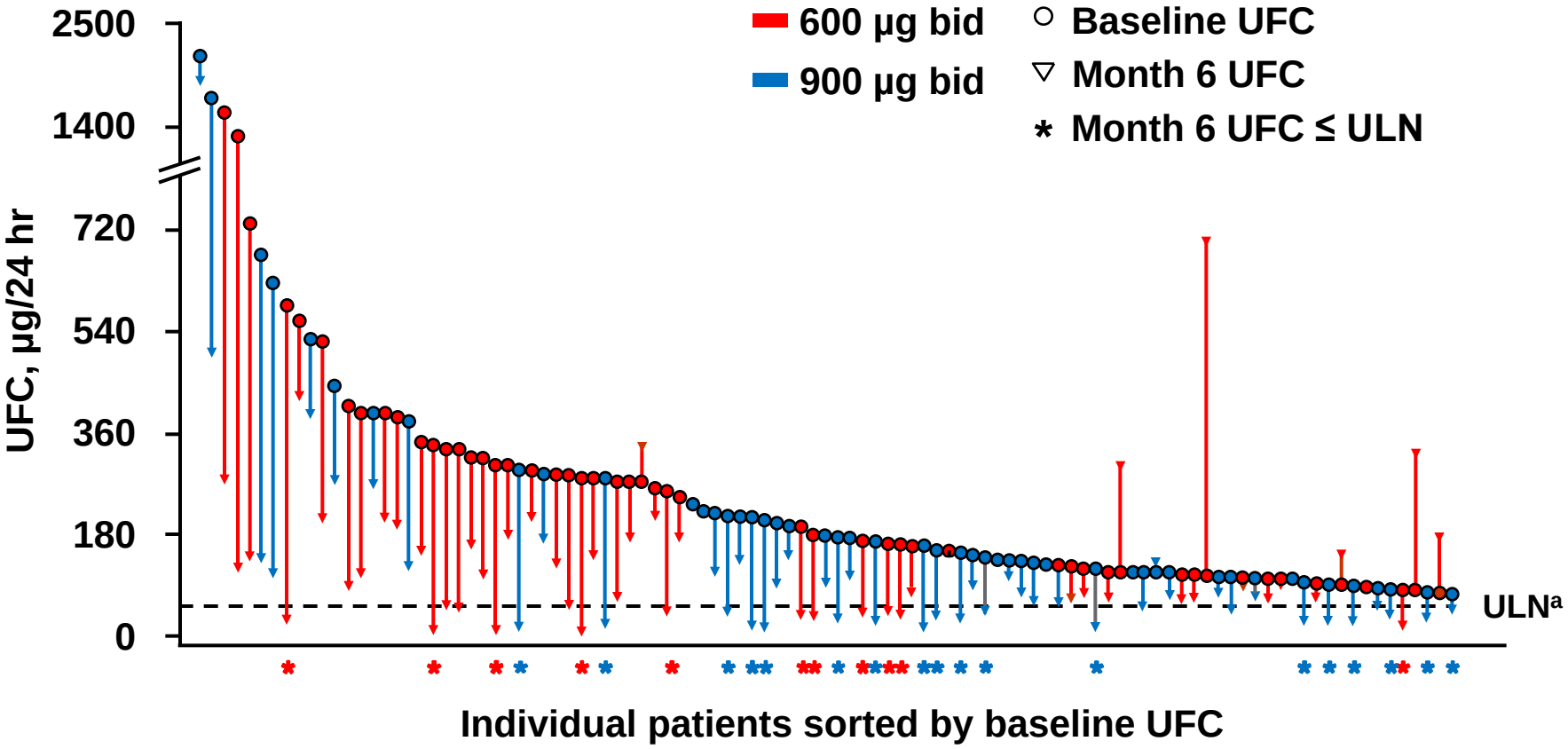
Adjusted Mean Percent Change From Baseline in UFC



Based on repeated measures mixed model with dose, time, baseline, and dose*time as fixed effects, and patient as random effect nested within dose.

Change in UFC From Baseline to Month 6

Patients With Baseline and Month 6 UFC Measurements (n=103)



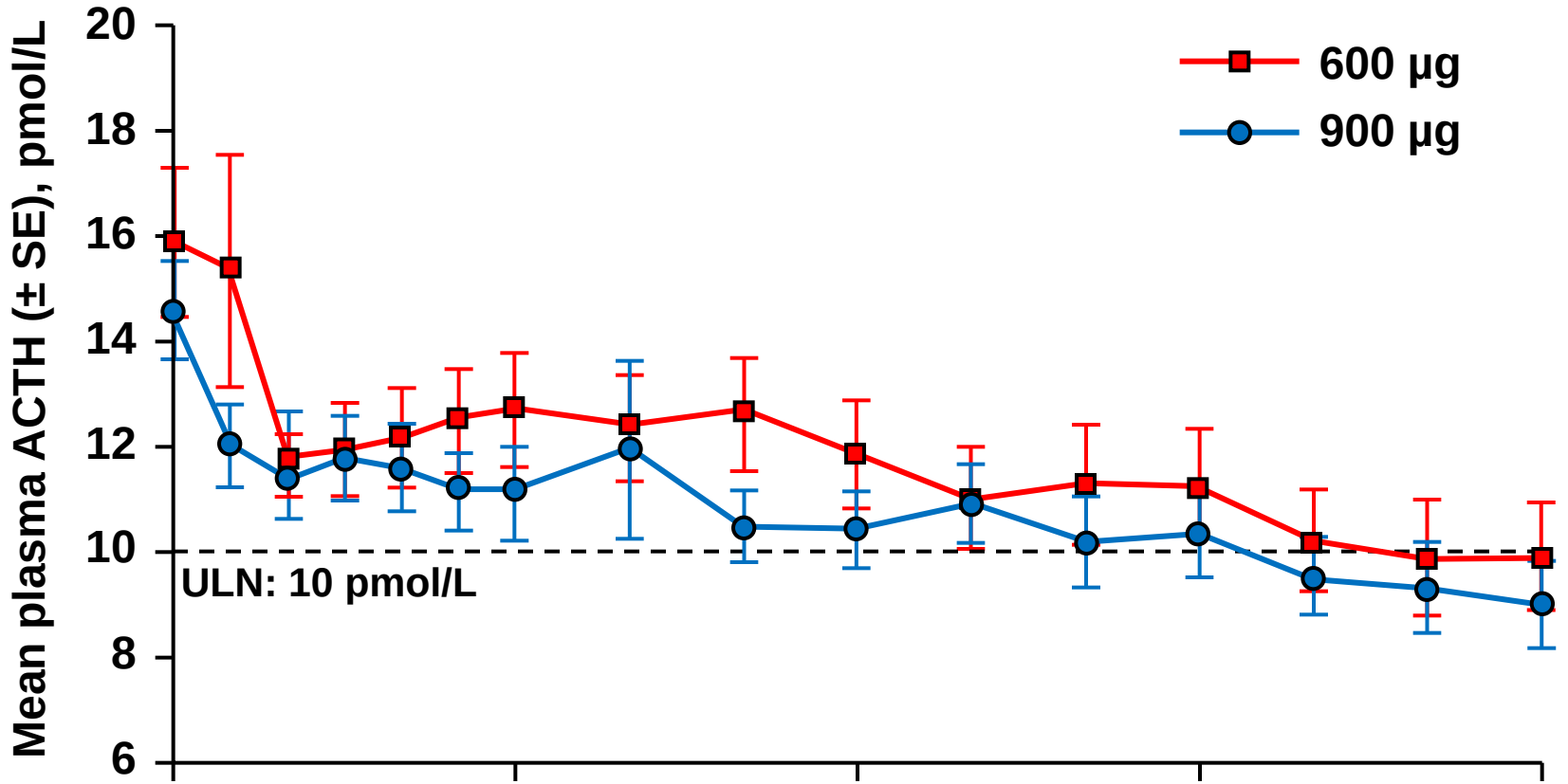
Median percent UFC change from baseline was –47.9% in both groups

[a] Reference line is the upper limit normal UFC, which is 52.5 µg/24h (145 nmol/24 hr).

Colao A, et al. *N Engl J Med*. 2012;366:914-924.

Plasma ACTH Levels

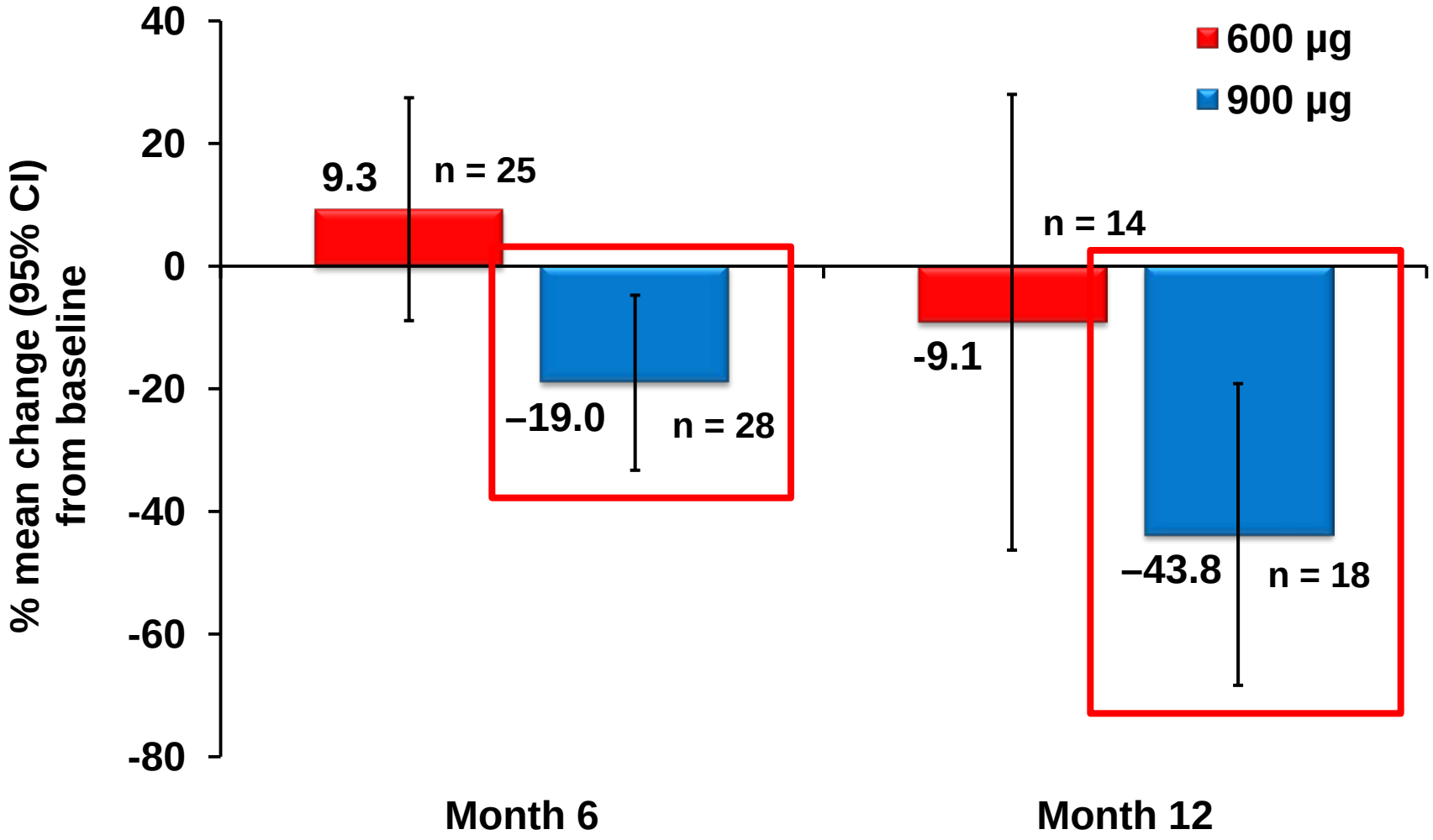
Study B2305



Patients					
600 µg	82	69	58	46	39
900 µg	80	67	56	48	39

Change in Tumor Volume From Baseline

Study B2305



Clinical Endpoints

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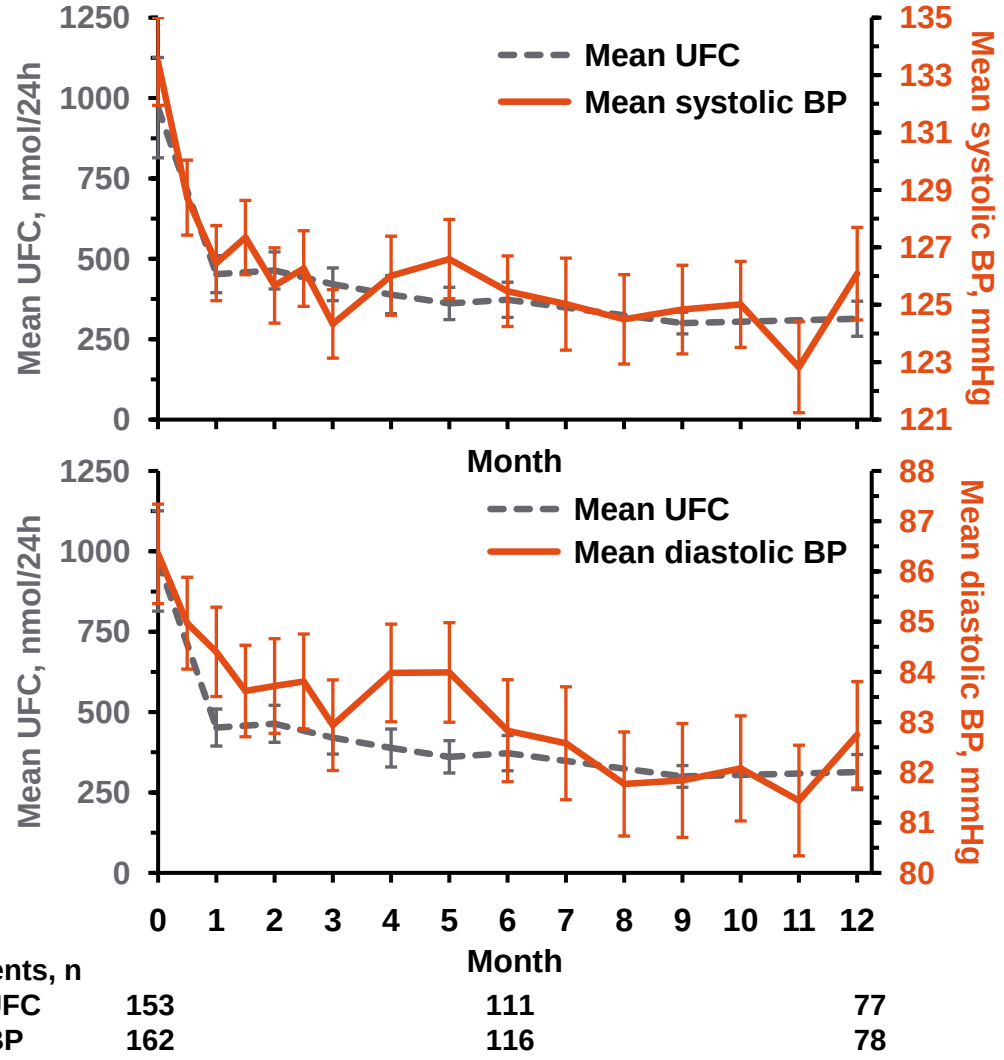
Changes in UFC and Blood Pressure

Study B2305



SBP (M12) –6.1 mmHg
(95% CI: –9.8, –2.4)

DBP (M12) –3.7 mmHg
(95% CI: –6.2, –1.2)

Colao A, et al. *N Engl J Med*. 2012;366:914-24.

Changes in SBP and DBP from Baseline to Month 12

Study B2305—Overall Patient Population and Stratified by Baseline Hypertension and Use of Antihypertensive Medication

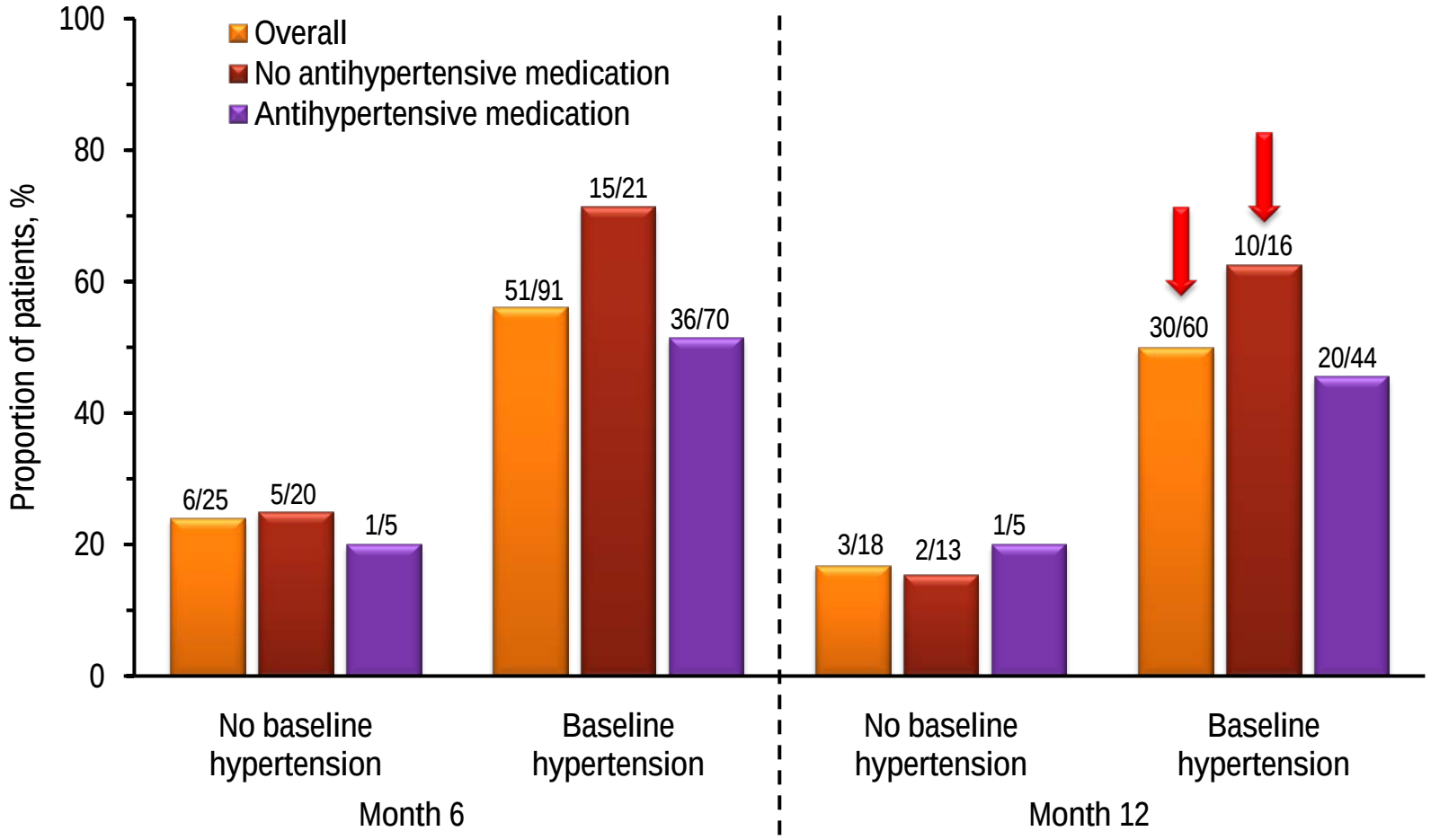
- Significant improvements in SBP and DBP from baseline to month 12 were seen in patients with baseline hypertension

	Mean change in SBP, mmHg (95% CI)	Mean change in DBP, mmHg (95% CI)
Overall, n = 78	–6.1 (–9.8, –2.4)	–3.7 (–6.2, –1.2)
Hypertension at baseline	–8.0 (–12.4, –3.6)	–4.7 (–7.7, –1.7)
No antihypertensive medication use during study, n = 16	–13.2 (–20.0, –6.4)	–7.3 (–12.9, –1.7)
Antihypertensive medication use during study, n = 44	–6.1 (–11.5, –0.7)	–3.7 (–7.2, –0.2)
No hypertension at baseline	0.2 (–6.1, 6.4)	–0.4 (–4.6, 3.9)
No antihypertensive medication use during study, n = 13	–0.3 (–8.2, 7.6)	–0.9 (–6.2, 4.5)
Antihypertensive medication use during study, n = 5	1.5 (–9.1, 12.1)	1.0 (–6.0, 8.0)

Pivonello R, et al. Presented at ENDO, Houston, Texas, USA, 23–26 June 2012. Abstract SUN-737.

Patients With a > 5 mmHg Decrease in DBP from Baseline to Months 6 and 12, by Baseline Hypertension and Use of Antihypertensive Medication During Study

Study B2305

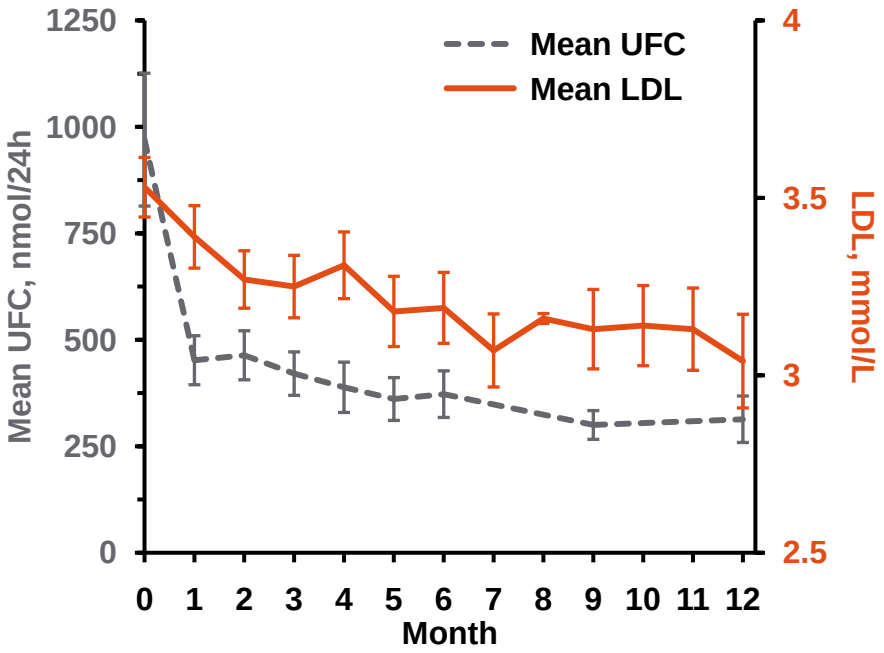


Presented at ENDO, Houston, Texas, USA, 23–26 June 2012.

Changes in UFC and LDL and Triglycerides

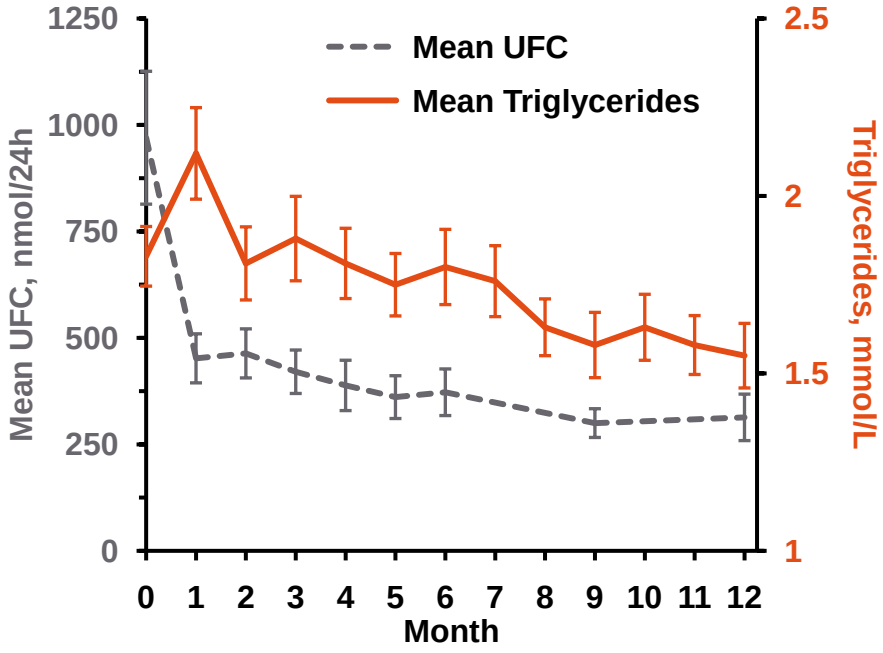
Study B2305

LDL



Patients, n			
---- UFC	153	111	77
–– LDL	162	114	79

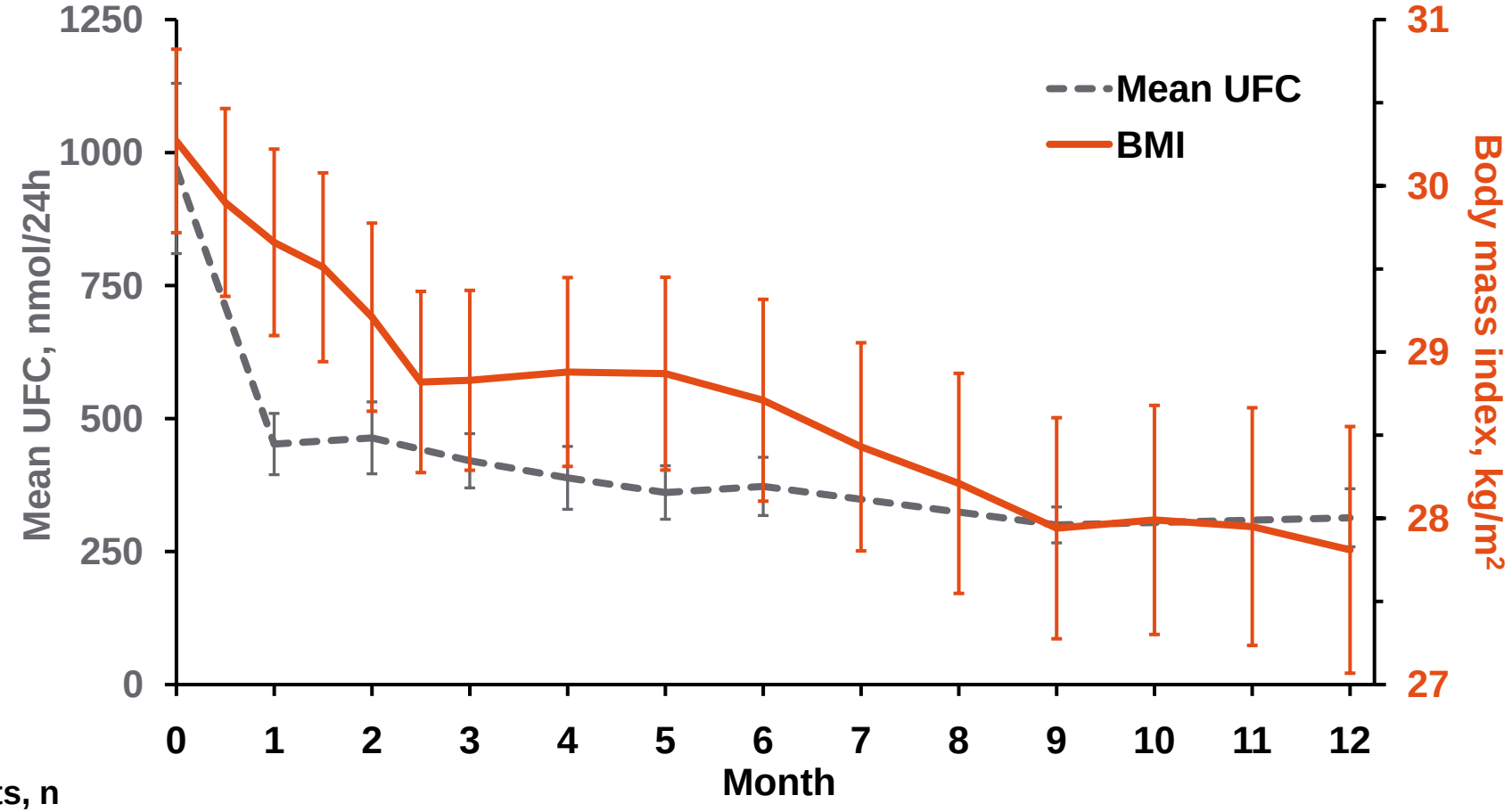
Triglycerides



Patients, n			
---- UFC	153	111	77
–– TG	162	114	79

Mean UFC and Body Mass Index up to Month 12

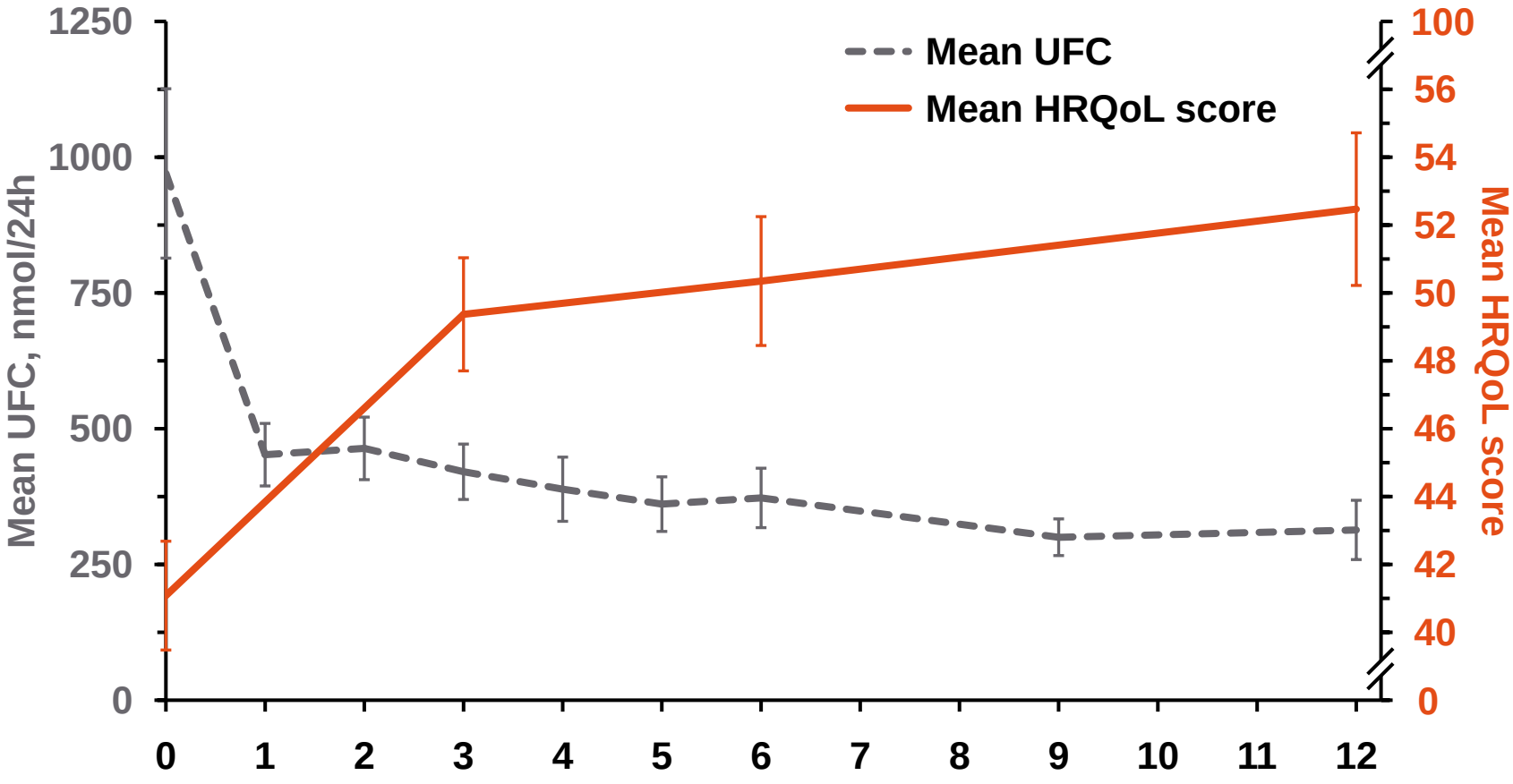
Study B2305—Full Analysis Set



Patients, n			
---- UFC	153	111	77
–– BMI	162	116	79

Changes in UFC and CushingQoL

Study B2305

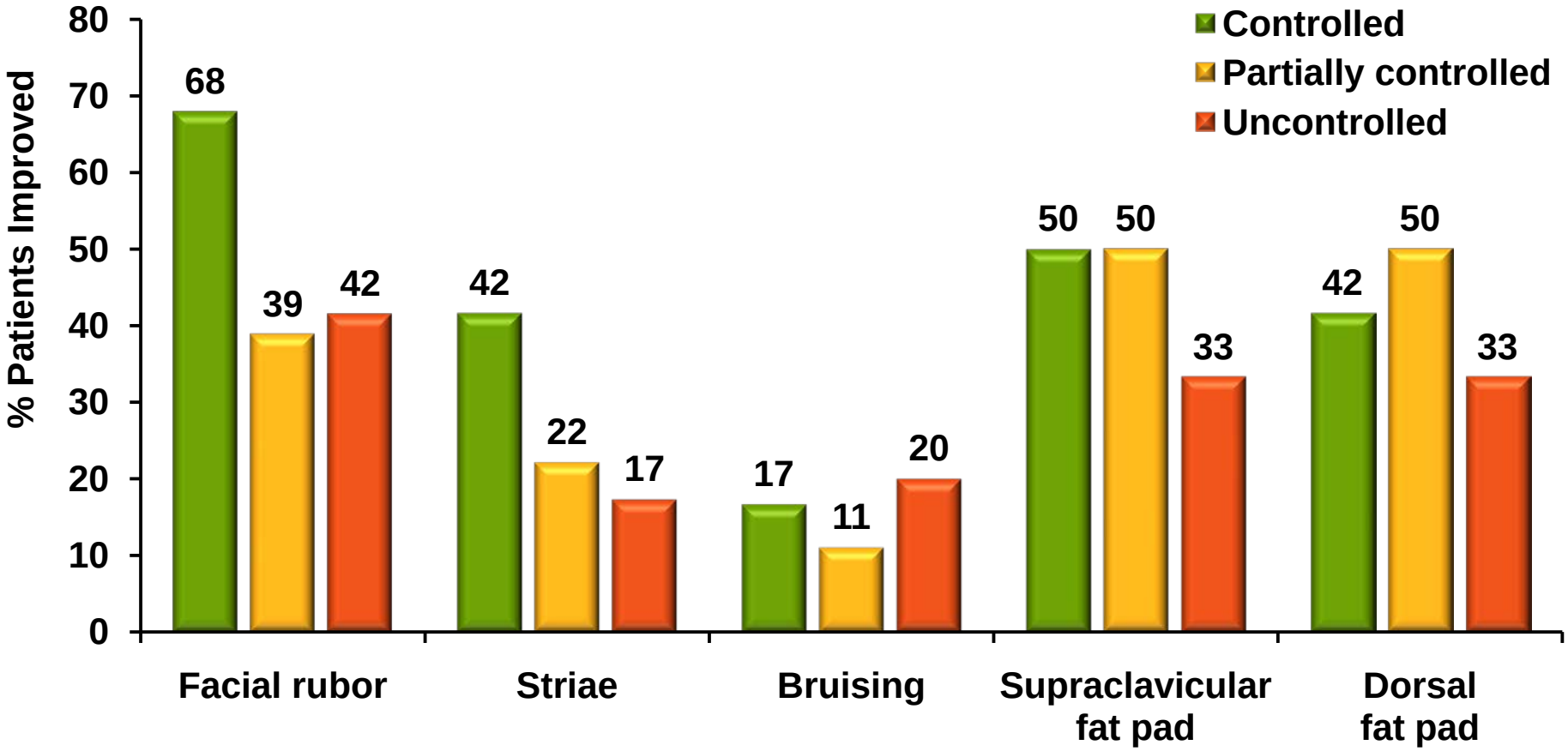


Patients, n			
---- UFC	153	111	77
–– HRQoL	159	112	76

CushingQoL = Health-related quality of life instrument specific for patients with Cushing's syndrome.

Patients With Improvement in Physical Features of Hypercortisolism (Month 6)

Study B2305



Patient improved if Month 6 is less severe than at baseline.

Presentation Overview

- Clinical Pharmacology
- Study Design and Efficacy Results
  - Phase II Study B2208
  - Phase III Study B2305
- Efficacy Conclusions

Efficacy Conclusions
Study B2305

- Pasireotide effectively lowered UFC levels in patients with Cushing's disease
  - Pasireotide (900 µg bid) met primary endpoint of UFC normalization at 6 months
  - UFC reduction is rapid, robust, and sustained at Months 6 and 12
  - Majority of patients had a decline in UFC levels
- Pasireotide effectively reduces ACTH levels in patients with Cushing's disease
- UFC reductions in patients with Cushing's disease associated with clinically meaningful improvements in blood pressure, blood lipids, body weight, and quality of life

Pasireotide
Safety and Risk Minimization

Pablo Cagnoni, MD

Novartis Pharma

NOVARTIS

Presentation Overview—Safety

- Overall safety in study B2305
  - Drug exposure and discontinuations
  - AEs and SAEs
- Special safety topics and risk minimization
  - Liver function abnormalities
  - QT prolongation
  - Hypocortisolism/Cortisol Withdrawal Syndrome
  - Hyperglycemia
- Overall conclusions

Drug Exposure

Study B2305

Exposure Category, months	Patients, n (%) 600 µg n = 82	900 µg n = 80
≥ 1	76 (92.7)	74 (92.5)
≥ 3	68 (82.9)	64 (80.0)
≥ 6	55 (67.1)	55 (68.8)
≥ 9	45 (54.9)	45 (56.3)
≥ 12	28 (34.1)	35 (43.8)
≥ 18	15 (18.3)	11 (13.8)
≥ 24	6 (7.3)	7 (8.8)
Mean, mo (SD)	10.66 (7.645)	10.89 (8.232)
Median, mo (min - max)	10.58 (0.03 - 31.1)	10.22 (0.03 - 37.8)

Adverse Events Reported in > 15% of Patients

Study B2305

	Patients, %			
	600 µg (n = 82)		900 µg (n = 80)	
Preferred Term[a]	All Grades	Grade 3/4	All Grades	Grade 3/4
Diarrhea	58.5	3.7	57.5	2.5
Nausea	46.3	1.2	57.5	3.8
Hyperglycemia	37.8	9.8	42.5	16.3
Cholelithiasis	30.5	1.2	30.0	1.3
Headache	28.0	1.2	28.8	2.5
Abdominal pain	23.2	1.2	25.0	2.5
Fatigue	14.6	1.2	23.8	2.5
Diabetes mellitus	15.9	7.3	20.0	7.5
Asthenia	15.9	2.4	6.3	2.5

[a] **A patient with multiple AEs could be counted in more than one category.**

AEs Leading to Discontinuation

Study B2305

	Patients, n (%)		
	600 µg n = 82	900 µg n = 80	Overall N = 162
Any AE(s)	**13 (15.9)**	**15 (18.8)**	**28 (17.3)**
Any AE(s) of special interest	12 (14.6)	12 (15.0)	24 (14.8)
Hyperglycemia-related AEs	4 (4.9)	6 (7.5)	10 (6.2)
Liver safety-related AEs	4 (4.9)	2 (2.5)	6 (3.7)
Diarrhea-related AEs	1 (1.2)	2 (2.5)	3 (1.9)
Nausea-related AEs	1 (1.2)	1 (1.3)	2 (1.2)
Bradycardia-related AEs	0	1 (1.3)	1 (0.6)
Gallbladder- and biliary-related AEs	1 (1.2)	0	1 (0.6)
Hypocortisolism-related AEs	0	1 (1.3)	1 (0.6)
Pancreatitis-related AEs	1 (1.2)	0	1 (0.6)
QT-prolongation–related AEs	0	1 (1.3)	1 (0.6)
Other AEs (not classified as “special interest”)[a]	1 (1.2)	3 (3.8)	4 (2.5)

[a] Pituitary tumor benign, cranial nerve paralysis, tongue paralysis, fecal incontinence, asthenia, blood immunoglobulin E increased, tremor, pregnancy, confusional state, urine incontinence, hypotension, urticaria.

Serious Adverse Events

Study B2305

	Patients, n (%)		
	600 µg n = 82	900 µg n = 80	Overall N = 162
Serious adverse events	**19 (23.2)**	**21 (26.3)**	**40 (24.7)**
Study drug related	7 (8.5)	12 (15.0)	19 (11.7)
Discontinued	3 (3.7)	5 (6.3)	8 (4.9)
Deaths[a]	**0**	**0**	**0**
SAEs ≥ 2% in any group			
Pituitary-dependent Cushing's syndrome[b]	3 (3.7)	3 (3.8)	6 (3.7)
Diabetes mellitus	1 (1.2)	3 (3.8)	4 (2.5)
Hyperglycemia	1 (1.2)	3 (3.8)	4 (2.5)
Cholelithiasis	3 (3.7)	1 (1.3)	4 (2.5)
Pituitary tumor benign[b]	1 (1.2)	2 (2.5)	3 (1.9)
Adrenal insufficiency	0	2 (2.5)	2 (1.2)

[a] No deaths during active treatment; 1 death during screening phase; 1 death reported ~2 months after discontinuation.

[b] Events were reported as SAEs because the patients were hospitalized for surgery.

Presentation Overview—Safety

- Overall safety in study B2305
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Elevations in Liver Tests

Study B2305

Test	Patients, n (%)	
	600 µg n = 79	900 µg n = 77
ALT or AST > 3 × ULN	6 (7.6)	2 (2.6)
ALT or AST > 5 × ULN	1[a] (1.3)	0
ALT or AST > 10 × ULN	0	0
TBIL ≥ 2 × ULN	0	0

- 6 patients discontinued treatment because of elevations in liver enzymes

[a] **Patient also included in ALT/AST > 3xULN category.**

Elevations in Liver Tests

Studies Other Than B2305

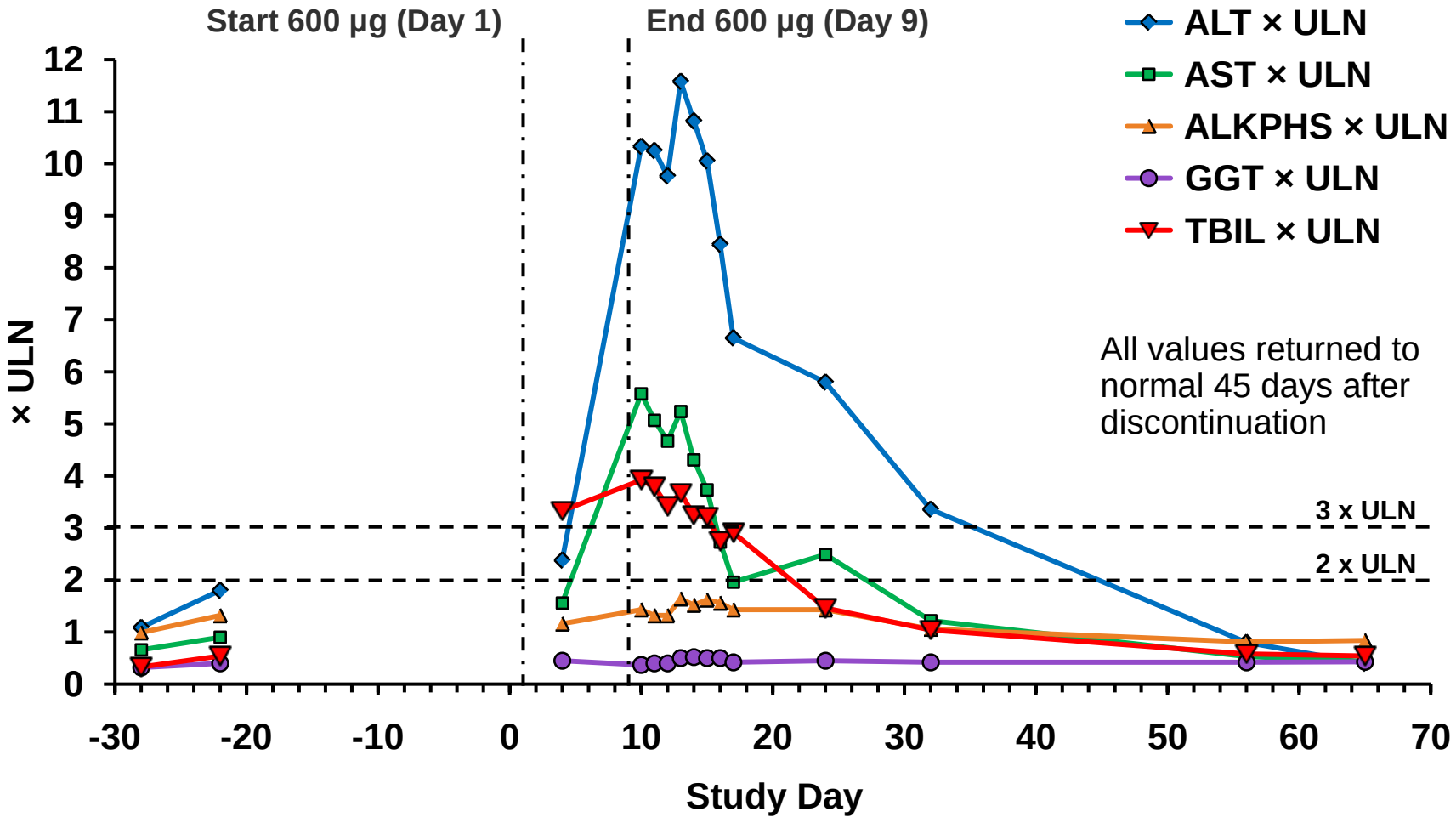
	Healthy volunteers N = 654	Patients N = 156
ALT or AST > 3 × ULN	16 (2.4)	6 (3.8)
ALT or AST > 5 × ULN	3 (0.5)	4 (2.6)
ALT or AST > 10 × ULN	—	3 (1.9)
TBIL ≥ 2 × ULN	17[a] (2.6)	2 (1.3)
Concurrent elevation of transaminases > 3 × ULN and total bilirubin ≥ 2 × ULN	3 (0.5)	0

Note: LFTs were routinely tested after 5 to 10 days only in few studies.

[a] Including 7 patients with pre-existing liver disease and elevations of total bilirubin.

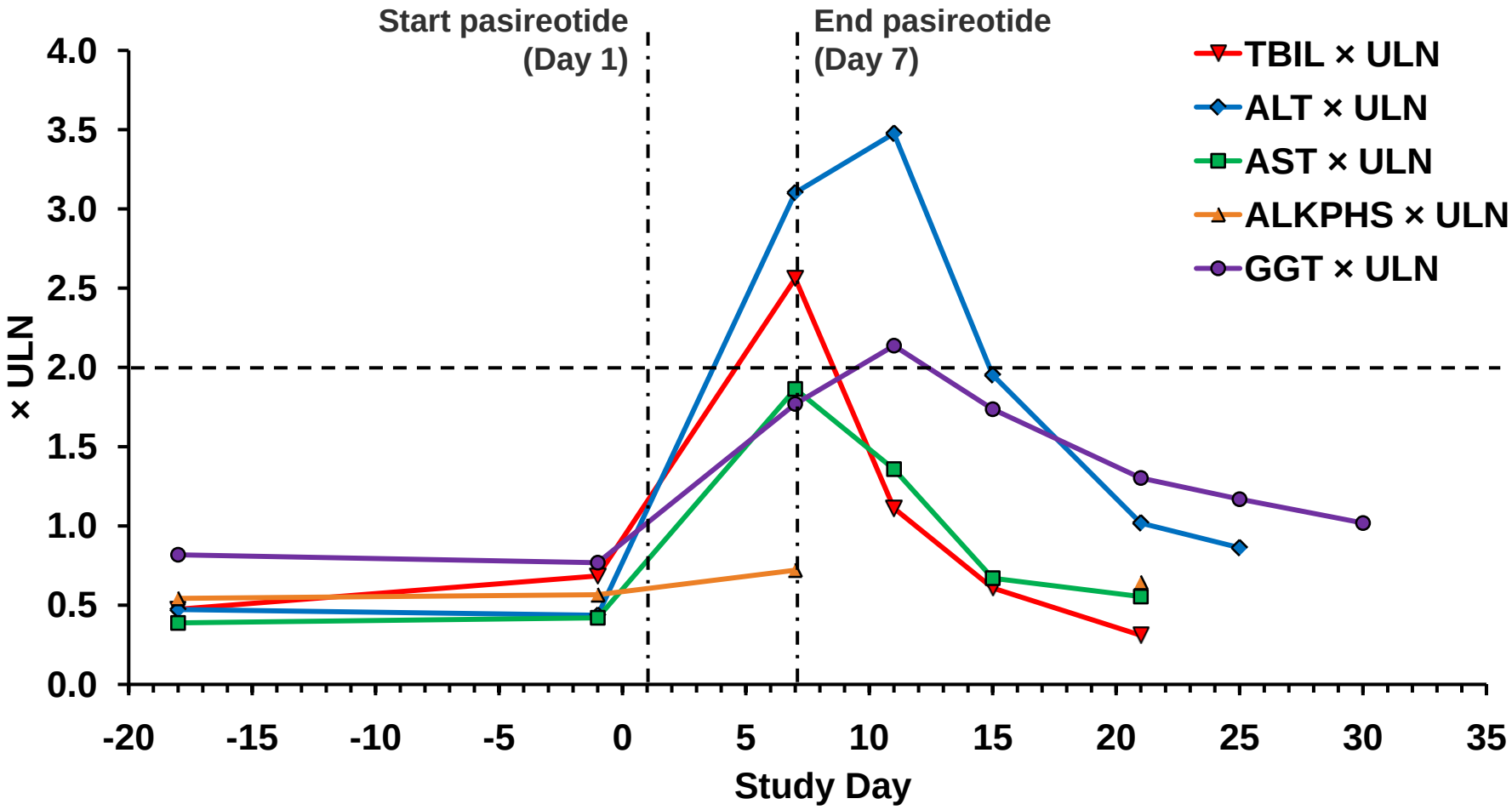
Concurrent Elevation of Bilirubin, ALT, AST

Compassionate Use Case



Concurrent Elevation of Bilirubin, ALT, AST

Healthy Volunteer, B2124-0001/10116



Treated with pasireotide 600 µg bid alone for 7 days.
× ULN = fold of upper limit of normal.

Hepatic Safety
Summary of Findings

- Hepatic safety profile consistent with class effect of somatostatin analogues
  - Small, transient elevations in aminotransferases
  - Elevations in bilirubin uncommon
- Across pasireotide clinical development program, 4 cases of concurrent elevation of transaminases > 3 x ULN and total bilirubin ≥ 2 x ULN
  - Not typical of severe drug-induced liver injury

Key Hepatic Risk Minimization Activities

- Monitor liver chemistry prior to treatment with pasireotide, after the first 1 to 2 weeks and after the first 2 to 3 months on treatment; afterwards, monitor as clinically appropriate
- Increased transaminase levels should be confirmed with a second liver function evaluation
  - If confirmed, frequent monitoring should be conducted until values return to pre-treatment levels
- Pasireotide treatment should be permanently discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver impairment or a sustained increase in AST, ALT, and/or bilirubin
  - Following discontinuation of treatment with pasireotide, patients should be monitored until resolution

Presentation Overview—Safety

- Overall safety in study B2305
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Categorical Analyses of QTcF

Study B2305

	600 µg n = 82		900 µg n = 80	
Calculated QTc (central read)	**Total**	**n (%)**	**Total**	**n (%)**
QTcF				
New[a] > 450 ms[b]	75	3 (4.0)	71	4 (5.6)
New[a] > 480 ms[b]	76	0	74	3 (4.1)
New[a] > 500 ms[b]	76	0	74	2 (2.7)
Increase > 30 ms[c]	77	23 (29.9)	74	28 (37.8)
Increase > 60 ms[c]	77	2 (2.6)	74	3 (4.1)

[a] As compared to the prior core baseline value.

[b] Total is the number of patients with a measurement at baseline (not meeting the abnormality criteria) and a post-baseline measurement.

[c] Total is the number of patients with a measurement at both baseline and post-baseline.

ECGs were to be obtained prior to the morning injection of pasireotide, per protocol.

Comprehensive Search for Events Indicative of Arrhythmogenic Potential

Study B2305

- AEs indicative of arrhythmogenic potential based on Torsades de Pointes (TdP)/QT prolongation SMQ with addition of preferred term "convulsion"

Preferred terms

- Cardiac arrest
- Cardiac death
- Cardiac fibrillation
- Cardio-respiratory arrest
- Convulsion
- Electrocardiogram QT interval abnormal
- Electrocardiogram QT prolonged
- Electrocardiogram U-wave abnormality
- Electrocardiogram U-wave biphasic
- Electrocardiogram repolarization abnormality
- Long QT syndrome
- Long QT syndrome congenital
- Loss of consciousness
- Sudden cardiac death
- Sudden death
- Syncope
- Torsades de pointes
- Ventricular arrhythmia
- Ventricular fibrillation
- Ventricular flutter
- Ventricular tachyarrhythmia
- Ventricular tachycardia

AEs Indicative of Arrhythmogenic Potential

Study B2305

	Patients, n (%)			
	600 µg n = 82		900 µg n = 80	
Preferred term	**All**	**Grade 3**	**All**	**Grade 3**
Electrocardiogram QT prolonged[a]	5 (6.1)	0	5 (6.3)	2 (2.5)
Syncope	1 (1.2)	1 (1.2)	2 (2.5)	1 (1.3)

- 1 patient discontinued due to SAE of "Electrocardiogram QT prolonged"

A patient with multiple occurrences of an AE under one dose level is counted only once in the AE category for that dose level.
A patient with multiple AEs is counted only once in the total row.
[a] Based on local ECG readings.

TQT Program Overview

- Study B2113 showed QTcF prolongation at MTD (1950 µg bid)
  - Maximum placebo-subtracted change from baseline 17.5 ms (90% CI: 15.53, 19.38)
  - No QTcF outliers (> 480 ms or change from baseline > 60 ms)
  - Limitations: single dose, no time-matched pre- and post-dose ECGs
- Study B2125 addressed limitations of B2113
  - 24-hour Holter-ECG monitoring
  - Maximum placebo-subtracted change from baseline in QTcI
    - 600 µg bid (therapeutic): 13.19 ms (90% CI: 11.38, 15.01)
    - 1950 µg bid (supratherapeutic): 16.12 ms (90% CI: 14.30, 17.95)

Pasireotide Program-Wide QT/QTc Related Analysis

Studies Analyzed for QT/QTc Outlier Events	Studies, n	Patients/HV With Notable QTcF Interval Outlier Values[a]
All studies	**16**	**11/829 (1.3%)**
Healthy volunteers	9	3/537
Patients (Cushing's disease, acromegaly)	6	6/258
PK in hepatic impairment	1	2/34[b]

HV = healthy volunteers.

[a] New QTcF > 480 ms or new QTcF > 500 ms or QTcF change from baseline > 60 ms.

[b] 2/19 patients with hepatic impairment; 0/15 age-, sex-, weight-matched controls.

Summary of QT Prolongation

- Low incidence of notable QTcF outliers in B2305
- Low incidence of AEs of arrhythmogenic potential in B2305
- Effect on QT/QTc characterized in 2 TQT studies
  - Covered therapeutic exposures in patients with Cushing's disease
  - QTcI prolongation 13 to 16 ms observed, no outliers > 500 ms

Key QT Prolongation Risk Minimization Activities

- Pasireotide should be used with caution in patients at risk of developing QT prolongation
- Baseline ECG is recommended prior to pasireotide treatment and as clinically indicated
- Correct hypokalemia and hypomagnesemia prior to pasireotide administration and monitor periodically during therapy

Presentation Overview—Safety

- Overall safety in study B2305
  - Drug exposure and discontinuations
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- Special safety topics and risk minimization
  - Liver function abnormalities
  - QT prolongation
  - Hypocortisolism/Cortisol Withdrawal Syndrome
  - Hyperglycemia
- Overall conclusions

Hypocortisolism/Cortisol Withdrawal Syndrome

Study B2305

- Expected with effective therapies for Cushing's disease
- 19 AEs in 13 (8.0%) patients[a]
  - 8 of 13 patients controlled or partially controlled at Month 6
- 2 patients with an SAE, 1 patient discontinued due to AE
- No difference between dose groups
- With the exception of 1 patient, all had at least 1 UFC ≤ LLN during study
- All AEs (with the exception of 2 patients) resolved with dose reduction or temporary replacement with glucocorticoids

[a] Preferred terms: adrenal insufficiency, blood cortisol decreased, urine-free cortisol decreased, and secondary adrenal insufficiency.

Key Hypocortisolism Risk Minimization Activites

- Monitor and provide guidance to patients on signs and symptoms associated with hypocortisolism/Cortisol Withdrawal Syndrome
- If hypocortisolism develops
  - Temporary dose reduction/interruption
  - Consider exogenous steroid replacement therapy

Presentation Overview—Safety

- Overall safety in study B2305
  - Drug exposure and discontinuations
  - AEs and SAEs
- Special safety topics and risk minimization
  - Liver function abnormalities
  - QT prolongation
  - Hypocortisolism/Cortisol Withdrawal Syndrome
  - Hyperglycemia
- Overall conclusions

Baseline Diabetic Status

Study B2305

Diabetic Status at Baseline	Patients, n (%)		
	600 µg N = 82	900 µg N = 80	Overall N = 162
Normal glucose tolerance	35 (42.7)	32 (40.0)	67 (41.4)
Pre-diabetic	18 (22.0)	21 (26.3)	39 (24.1)
Diabetic	28 (34.1)	27 (33.8)	55 (34.0)
Missing	1 (1.2)	0	1 (0.6)

2010 American Diabetes Association.
Diabetic: patients taking anti-diabetic medication or prior history of diabetes mellitus or HbA1c ≥ 6.5% or FPG ≥ 126 mg/dL.
Pre-diabetic: patients not qualifying as diabetic and with 100 mg/dL ≤ FPG < 126 mg/dL or 5.7% ≤ HbA1c < 6.5%.
Normal glucose tolerance: patients not qualifying as diabetic or pre-diabetic and with FPG < 100 mg/dL and/or HbA1c < 5.7%.
Missing: patients with no prior history of diabetes mellitus and not taking anti-diabetic medication and both FPG and HbA1c are missing.

Glucose Metabolism-related AEs, All Grades

Study B2305

	Patients, n (%)					
	600 µg (n = 82)			900 µg (n = 80)		
Preferred term[a]	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Total	61 (74.4)	19 (23.2)	0	57 (71.3)	19 (23.8)	2 (2.5)
Hyperglycemia	31 (37.8)	8 (9.8)	0	34 (42.5)	12 (15.0)	1 (1.3)
Diabetes mellitus	13 (15.9)	6 (7.3)	0	16 (20.0)	5 (6.3)	1 (1.3)
Glycosylated hemoglobin increased	10 (12.2)	1 (1.2)	0	8 (10.0)	0	0
Type 2 diabetes mellitus	10 (12.2)	4 (4.9)	0	5 (6.3)	3 (3.8)	0
Hypoglycemia	12 (14.6)	3 (3.7)	0	3 (3.8)	0	0
Blood glucose increased	6 (7.3)	0	0	3 (3.8)	0	0
Blood glucose decreased	1 (1.2)	0	0	4 (5.0)	0	0
Glucose tolerance impaired	2 (2.4)	0	0	2 (2.5)	0	0
Glycosuria	0	0	0	1 (1.3)	0	0

[a] **A patient with multiple AEs could be counted in more than one category.**

Changes From Baseline in Diabetic Status

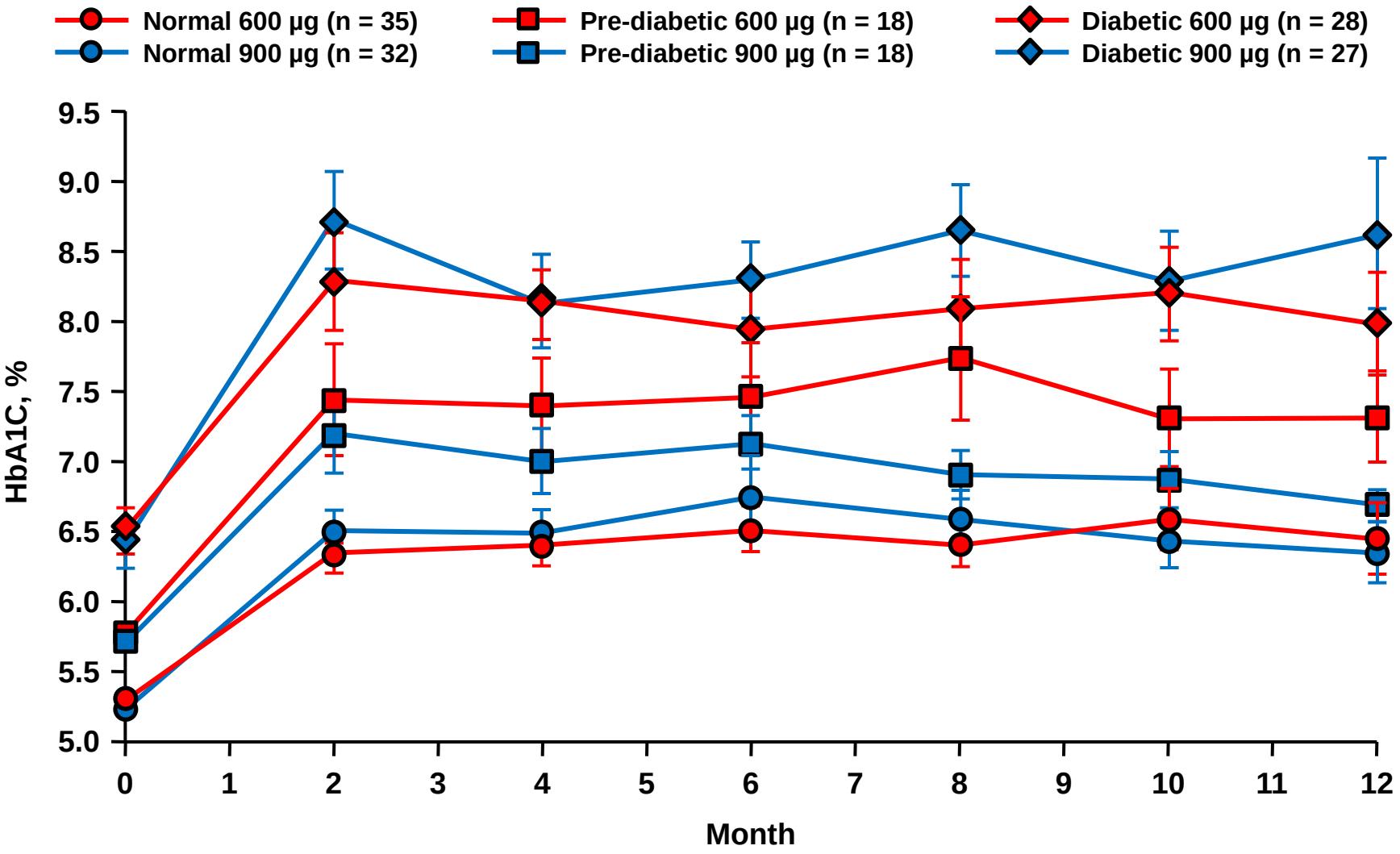
Study B2305

	Patients in Each Category at Last Assessment, n (%)			
Baseline Category	**Normal**	**Pre-diabetic**	**Diabetic**	**Missing**
Normal (n = 67)	14 (21)	29 (43)	23 (34)	1 (1.5)
Pre-diabetic (n = 39)	1 (3)	9 (23)	28 (72)	1 (3)
Diabetic (n = 55)	1 (2)	6 (11)	47 (85)	1 (2)
Missing (n = 1)	1 (100)	0	0	0

Post-baseline assessments defined as: Diabetic: HbA1c = 6.5% or FPG = 126 mg/dL; Pre-diabetic: Patients not qualifying as diabetic and with 100 mg/dL = FPG < 126 mg/dL or 5.7% = HbA1c < 6.5%; Normal glucose tolerance: Patients not qualifying as diabetic or pre-diabetic and with FPG < 100 mg/dL and/or HbA1c < 5.7%; Missing: both FPG and HbA1c are missing.

HbA1c Over Time by Baseline Diabetic Status

Study B2305



Mean FPG and HbA1c After Treatment Discontinuation[a]

Study B2305

	600 µg (n = 82)		900 µg (n = 80)	
	n[a]	Mean (SD)	n[a]	Mean (SD)
Fasting plasma glucose				
Baseline	27	97.8 (20.51)	30	98.6 (21.33)
Last value before discontinuation	27	126.1 (36.92)	30	133.7 (55.05)
Safety follow-up (4 wk)	27	102.2 (23.00)	30	104.5 (22.02)
HbA1c				
Baseline	25	6.0 (0.83)	29	5.8 (0.90)
Last value before discontinuation	25	7.7 (1.20)	29	7.6 (1.59)
Safety follow-up (4 wk)	25	6.9 (1.00)	29	6.8 (1.60)

[a] **Patients who had FPG or HbA1c measured at all 3 visits.**

Hyperglycemia Summary

Study B2305

- 58% of patients had diabetes or pre-diabetes at baseline
- Majority of patients had an increase in glycemia; HbA1c peaked at Month 2 and stabilized thereafter
- Diabetic patients randomized to 900 µg tended to have larger increases in HbA1c vs 600 µg group

Key Hyperglycemia Risk Minimization Activities

- Glycemic status (FPG/HbA1c) to be assessed prior to starting treatment
- In patients with impaired glucose tolerance or diabetes management and monitoring of hyperglycemia should be intensified prior to and during treatment
- Self-monitoring of blood glucose and/or FPG assessments to be done every week for the first 2 to 3 months and periodically thereafter, as clinically appropriate
- Initiation or adjustment of anti-diabetic treatment if hyperglycemia develops
  - Dose reductions or discontinuation if hyperglycemia persists

Hyperglycemia Mechanism and Management

Sonia Caprio, MD

Yale University School of Medicine

NOVARTIS

Disclosures

- Member of the Daiichi-Sankyo advisory board

Objectives

- Review of glucose homeostasis in Cushing's disease and role of somatostatin in glucose homeostasis
- Mechanistic studies of hyperglycemia during pasireotide treatment
  - Clamp study
  - Intervention study
- Planned intervention study in patients with Cushing's disease
- Conclusions

Patients With Cushing's Disease Are Predisposed to Changes in Glucose Homeostasis

- Chronically elevated cortisol levels causes insulin resistance and β-cell dysfunction that can lead to glucose intolerance or DM[a,b]

Morbidity	Prevalence at diagnosis, %[c]
IGT	21.3 - 64
Diabetes mellitus	20 - 36
Hypertension	55 - 85
Overweight (BMI 25-30)	21 - 48
Obesity (BMI > 30)	32 - 41
Dyslipidemia	37.5 - 71.4

[a] Newell-Price J, et al. *Lancet.* 2006;367(9522):1605-1617.
[b] Pivonello R, et al. *Endocrinol Metab Clin North Am.* 2008;37(1):135-149.
[c] Feelders R, et al. Presented at ENEA Cushing's Syndrome Workshop; Naples, Italy; December 2009.

Role of Somatostatin in Glucose Homeostasis

- Somatostatin is an inhibitor of both insulin and glucagon secretion[a]

	Somatostatin Receptors	
	sst_2	sst_5
sst expression in human pancreatic β-cells[b]	++	+++
sst expression in human pancreatic α-cells[b]	+++	+
Receptor binding affinity		
Pasireotide[c]	++	+++
Octreotide[c]	+++	+
Inhibition of insulin[d,e]	✓	✓
Inhibition of glucagon[f]	✓	

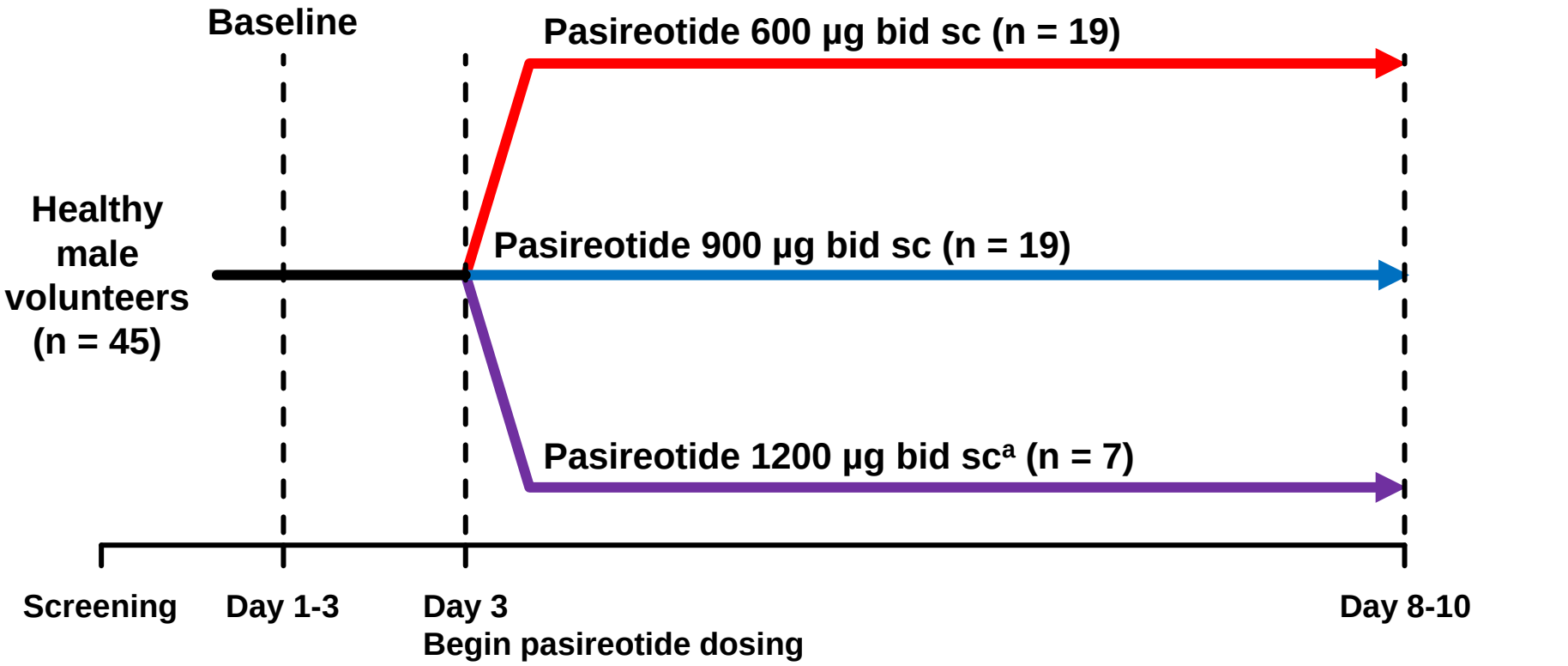
[a] Hauge-Evans AC, et al. *Diabetes.* 2009;58(2):403-411; [b] Kumar U, et al. *Diabetes*. 1999;48(1):77-85; [c] Adapted from Bruns C, et al. *Eur J Endocrinol*. 2002;146(5):707-716; [d] Zambre Y, et al. *Biochem Pharmacol.* 1999;57(10):1159-1164; [e] Singh V, et al. J *Clin Endocrinol Metab.* 2007;92(2):673-680; [f] Patel YC. *Front Neuroendocrinol.* 1999;20(3):157-198.

Mechanistic Studies of Hyperglycemia During Pasireotide Therapy

NOVARTIS

Study Design

Mechanistic Study B2216



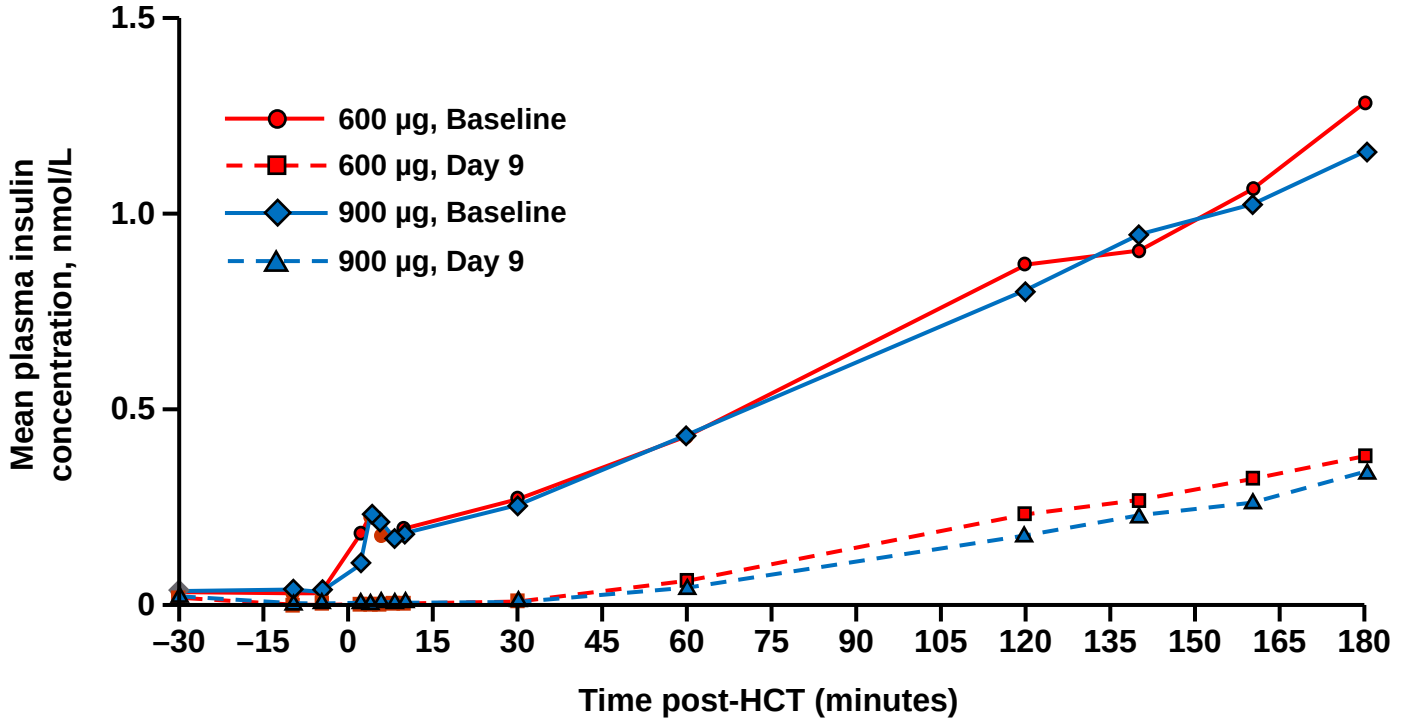
Baseline tests
- Day 1: OGTT
- Day 2: HGCT
- Day 3: HECT

End-of-study tests
- Day 8: OGTT
- Day 9: HGCT
- Day 10: HECT

OGTT = oral glucose tolerance test; HGCT = hyperglycemic clamp test; HECT = hyperinsulinemic euglycemic clamp test.
[a] 1200 µg bid sc arm was closed due to adverse events (AEs) of nausea and vomiting.

Hyperglycemic Clamp Test (HCT): Pasireotide Markedly Decreases Insulin

Mechanistic Study B2216



Insulin

Decreases in $AUC_{0–10min}$, $AUC_{10–180min}$ and $AUC_{0–180min}$ between baseline and day 9 were significant in both dose groups ($p < 0.001$)

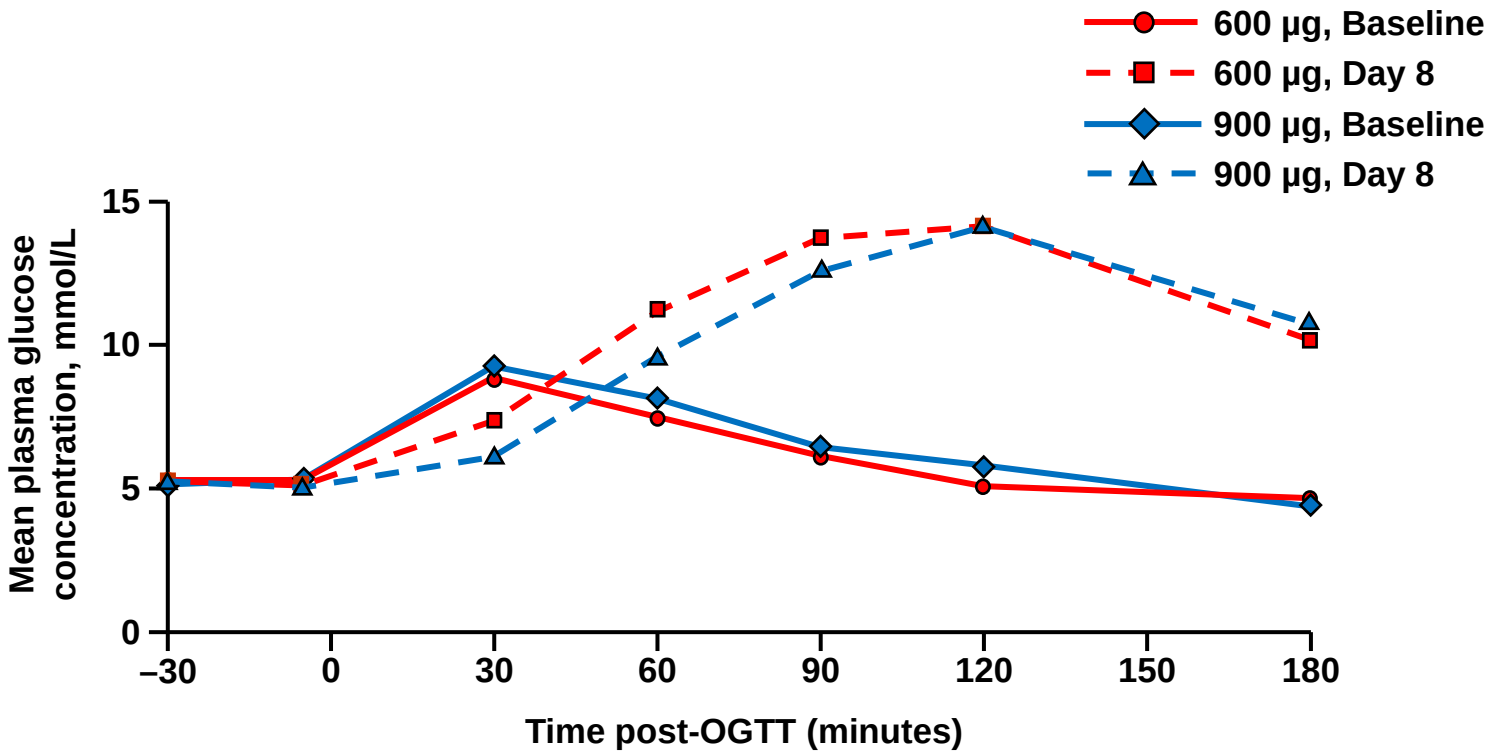
HCT = hyperglycemic clamp test.

OGTT—Pasireotide Increases Glucose

Mechanistic Study B2216

Glucose

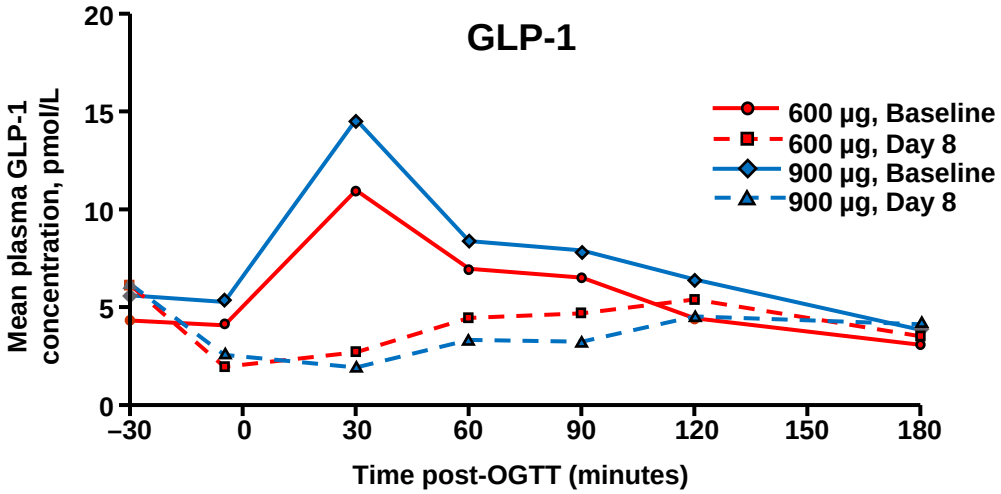
$AUC_{30–180min}$ and $AUC_{0–180min}$ significantly higher at day 8 than baseline ($p < 0.001$) in both dose groups

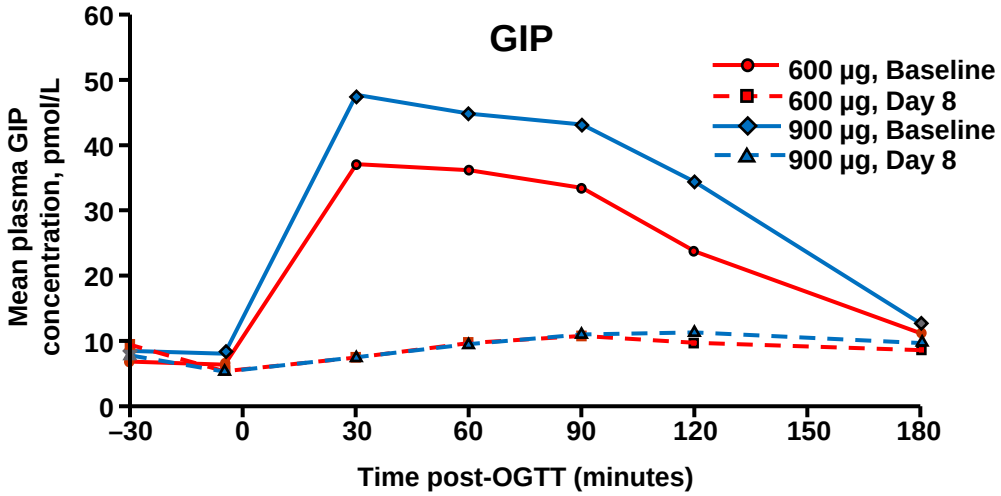


OGTT = oral glucose tolerance test.

OGTT—Pasireotide Decreases GLP-1 and GIP

Mechanistic Study B2216





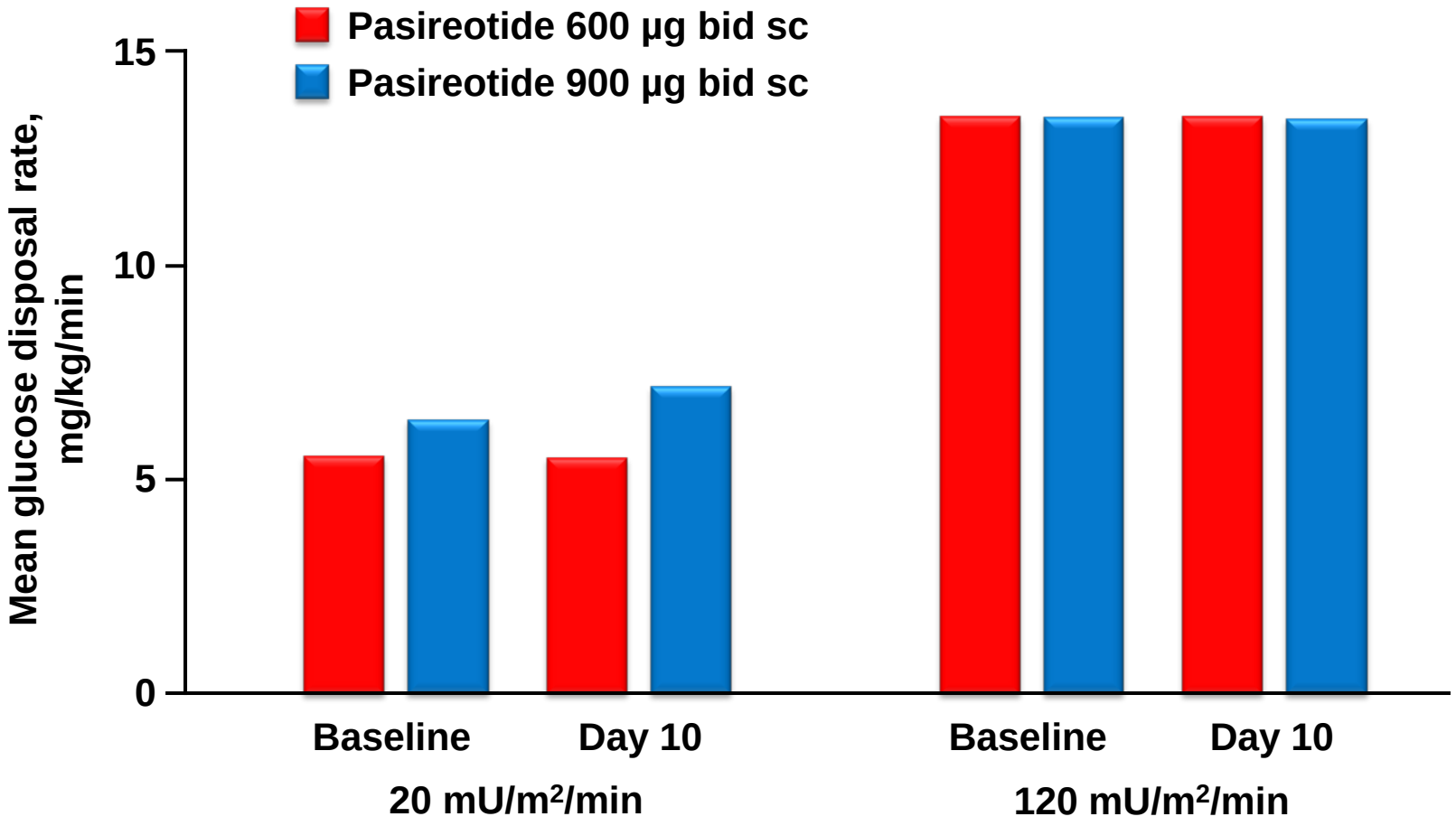
The following changes between baseline and day 8 were significant:

- **$AUC_{0–30min}$ ($p < 0.001$) and $AUC_{0–180min}$ ($p = 0.009$) for GLP-1 in the 600 µg group**
- **$AUC_{0–30min}$, $AUC_{30–180min}$ and $AUC_{0–180min}$ for GLP-1 in the 900 µg group ($p < 0.001$)**
- **All AUC parameters for GIP ($p < 0.001$) in both dose groups**

GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

Pasireotide Does Not Change Insulin Sensitivity During HECT

Mechanistic Study B2216



HECT = hyperinsulinemic euglycemic clamp test.

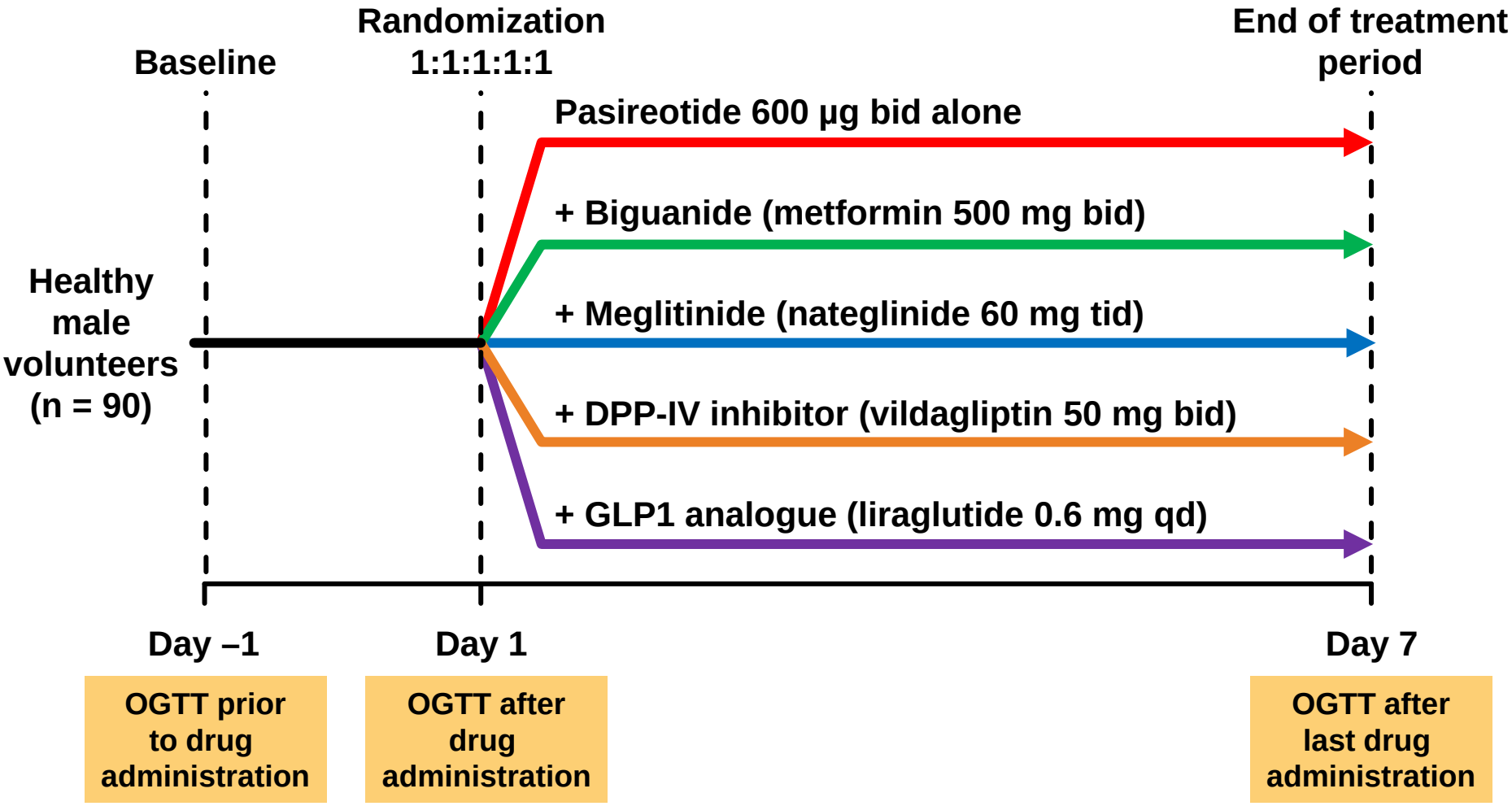
Summary

Mechanistic Study B2216

- The mechanisms of hyperglycemia seen with pasireotide sc at doses of 600 and 900 µg bid are related to
  - Significant decreases in insulin secretion, as observed following OGTT and HCT
    - Glucagon secretion is decreased but to a lesser degree
  - Significantly decreased incretin response, as observed following OGTT and HCT
- Pasireotide did not affect insulin sensitivity

Study Design

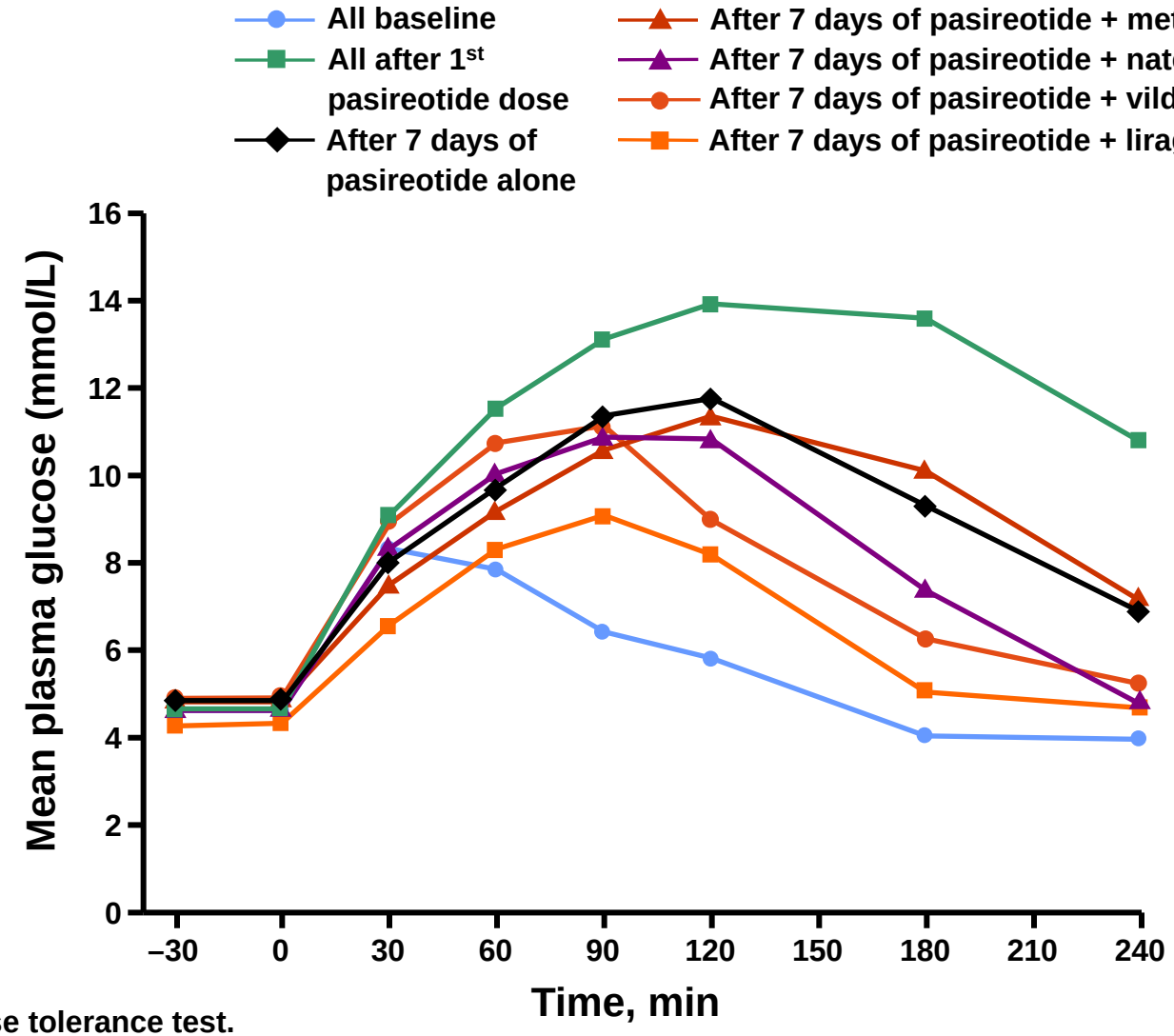
Management of Hyperglycemia Study B2124



OGTT = oral glucose tolerance test.

Changes in Glucose Levels During OGTT

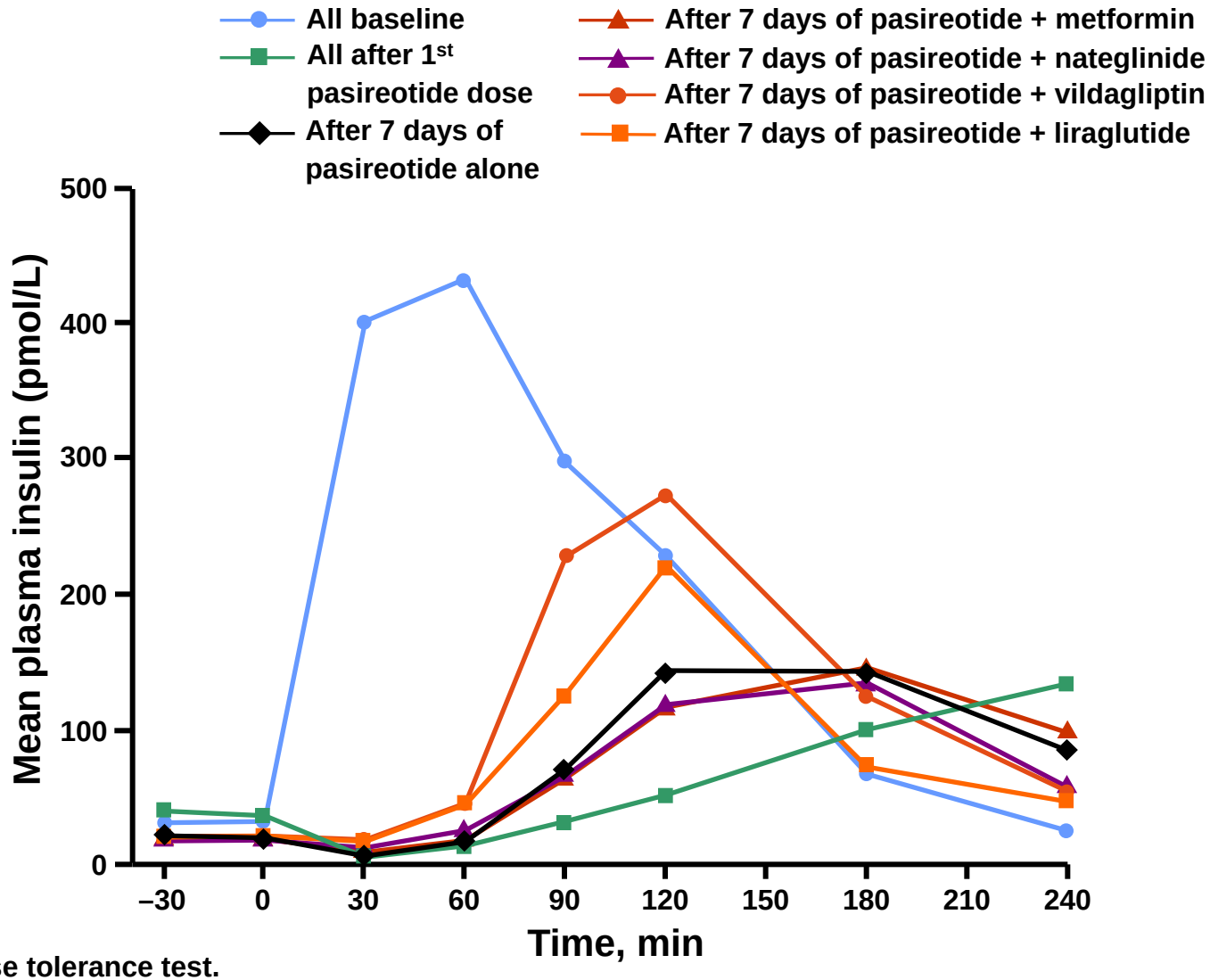
Management of Hyperglycemia Study B2124



OGTT = oral glucose tolerance test.

Changes in Insulin Levels During OGTT

Management of Hyperglycemia Study B2124



OGTT = oral glucose tolerance test.

Summary

Management of Hyperglycemia Study B2124

- Over a 7-day period in healthy volunteers
  - GLP-1 agonists and DPP-IV inhibitors seemed to be the most effective drugs to ameliorate pasireotide-induced hyperglycemia, followed by insulin secretagogues

Conclusions

- Pasireotide reduces insulin secretion and incretin response, without affecting insulin sensitivity
- GLP-1 agonists and DPP-4 inhibitors appear to be the most effective drugs to reduce glucose levels
- Hyperglycemia during treatment with pasireotide may be effectively managed
- Management should include
  - Proactive approach
  - Regular monitoring of blood glucose (including self monitoring)
  - Early intervention

Planned Intervention Study for Proactive Hyperglycemia Management

Study B2219[a]

- Multicenter, open-label, hyperglycemia management study in patients with Cushing's disease receiving pasireotide sc over 52 weeks (N = ~25)
  - Proactive evaluation of glycemia before and during treatment
    - Aim ADA/EASD treatment goals (HbA1c < 7%, FPG 100 to 130 mg/dL, and PPG < 180 mg/dL)
    - Tailored pharmacologic intervention
- Primary endpoint
  - Effect of intensive hyperglycemia management (ie, monitoring and intervention) on the change from baseline in HbA1c at 16 weeks
- Secondary endpoint
  - Change in glucose AUC during OGTT from Week 1 to Week 16

[a] **Post-approval commitment with EMA.**

Benefit:Risk Conclusions

Pablo Cagnoni, MD

Novartis Pharma

NOVARTIS

Efficacy Conclusions
Study B2305

- Pasireotide achieves clinically relevant decreases in UFC and ACTH levels in patients with Cushing's disease
  - Decreases are rapid and sustained
- Pasireotide achieves clinically meaningful improvements in signs and symptoms of Cushing's disease
  - Blood pressure
  - Body weight
  - Blood lipids
  - Physical features
  - Quality of life

Safety Conclusions

- Safety profile well-characterized, comparable to somatostatin analogues, with the exception of hyperglycemia
  - Majority of AEs were mild to moderate (Grade 1 to 2) and reversible
  - No deaths reported[a]
- Hyperglycemia was frequently reported
  - Effect stabilizes within 2 months of treatment
  - Reversible on treatment discontinuation
  - Mechanism is well understood
- Liver function abnormalities, prolongation of QT interval, and hypocortisolism were reported
- Recommendations for monitoring included in prescribing information

[a] No deaths during active treatment; 1 death during screening phase; 1 death reported ~2 months after discontinuation.

Additional Risk Minimization Activities

- Novartis proposes a Medication Guide as a part of pasireotide labeling
  - Will contain important information for patients on the safety and dosing of pasireotide
- Novartis plans to distribute pasireotide through a central pharmacy only
  - Physicians will submit prescriptions to have pasireotide delivered directly to the patient, along with the latest informational materials

Clinical Perspective on Pasireotide for the Treatment of Cushing's Disease

Shlomo Melmed, MB, ChB, MACP

Senior VP and Dean
Cedars-Sinai Medical Center
Los Angeles, CA

Disclosure Statement

- Senior Scientific Consultant to Novartis
- Scientific Consultant: Chiasma, Isis
- Clinical research support: Pfizer

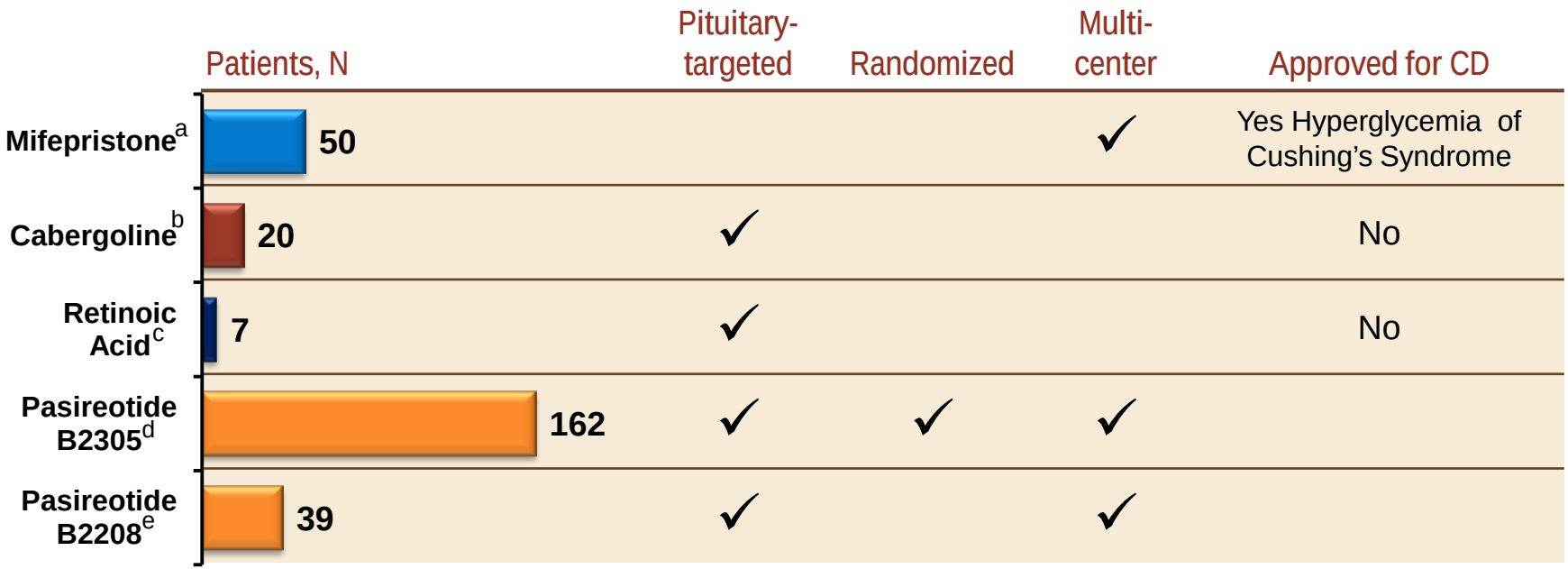
Cushing's Disease

- Orphan disease associated with significant morbidity and mortality
- Pituitary surgery is first-line treatment
- Unmet need for a pituitary-targeted medical therapy that
  - Normalizes ACTH and cortisol levels
  - Controls tumor growth
  - Improves signs and symptoms, and HRQoL
  - Reverses comorbidities and improves survival

Second-line Treatment Options

- Second pituitary surgery
- Pituitary radiation
- Bilateral adrenalectomy
- Medical therapy
  - Commonly used drugs in the US
    - Ketoconazole
    - Mifepristone
    - Cabergoline

Prospective Studies of Medical Treatments in Cushing's Disease



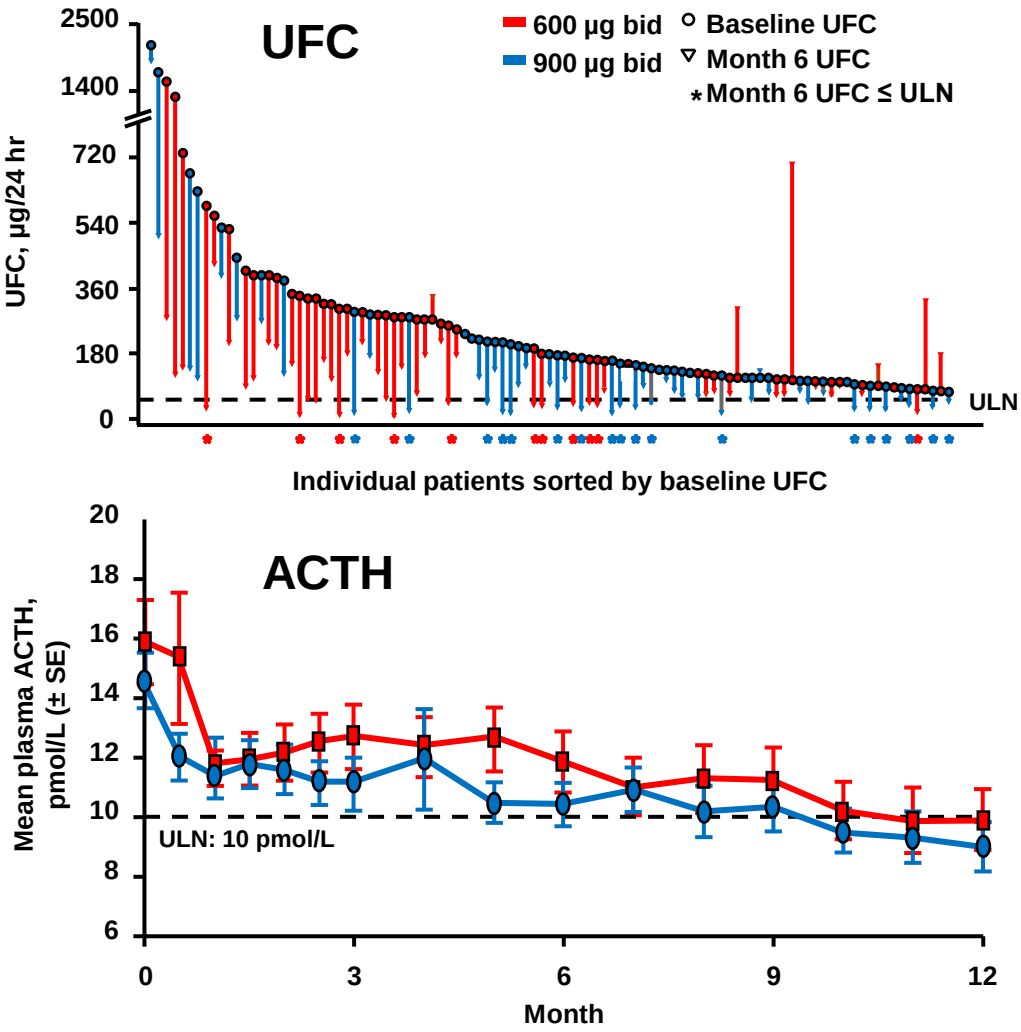
Monotherapy studies of ketoconazole, metyrapone, and mitotane are retrospective[f,g]

[a] Fleseriu M, et al. *J Clin Endocrinol Metab*. 2012;97(6):2039-2049; [b] Pivonello R, et al. *J Clin Endocrinol Metab.* 2009;94(1):223-230; [c] Giraldi FP, et al. *J Clin Edocrinol Metab*. 2012 [Epub ahead of print]; [d] Colao A, et al. *N Engl J Med.* 2012;366(10):914-924; [e] Boscaro M, et al. *J Clin Endocrinol Metab*. 2009;94(1):115-122; [f] Díez JJ & Iglesias P. *Mini Rev Med Chem*. 2007;7(5):467-480; [g] Castinetti F, et al. *Eur J Endocrinol*. 2008;158(1):91-99.

Biochemical Benefits of Pasireotide in Patients With Cushing's Disease

Reduction in UFC and ACTH Levels

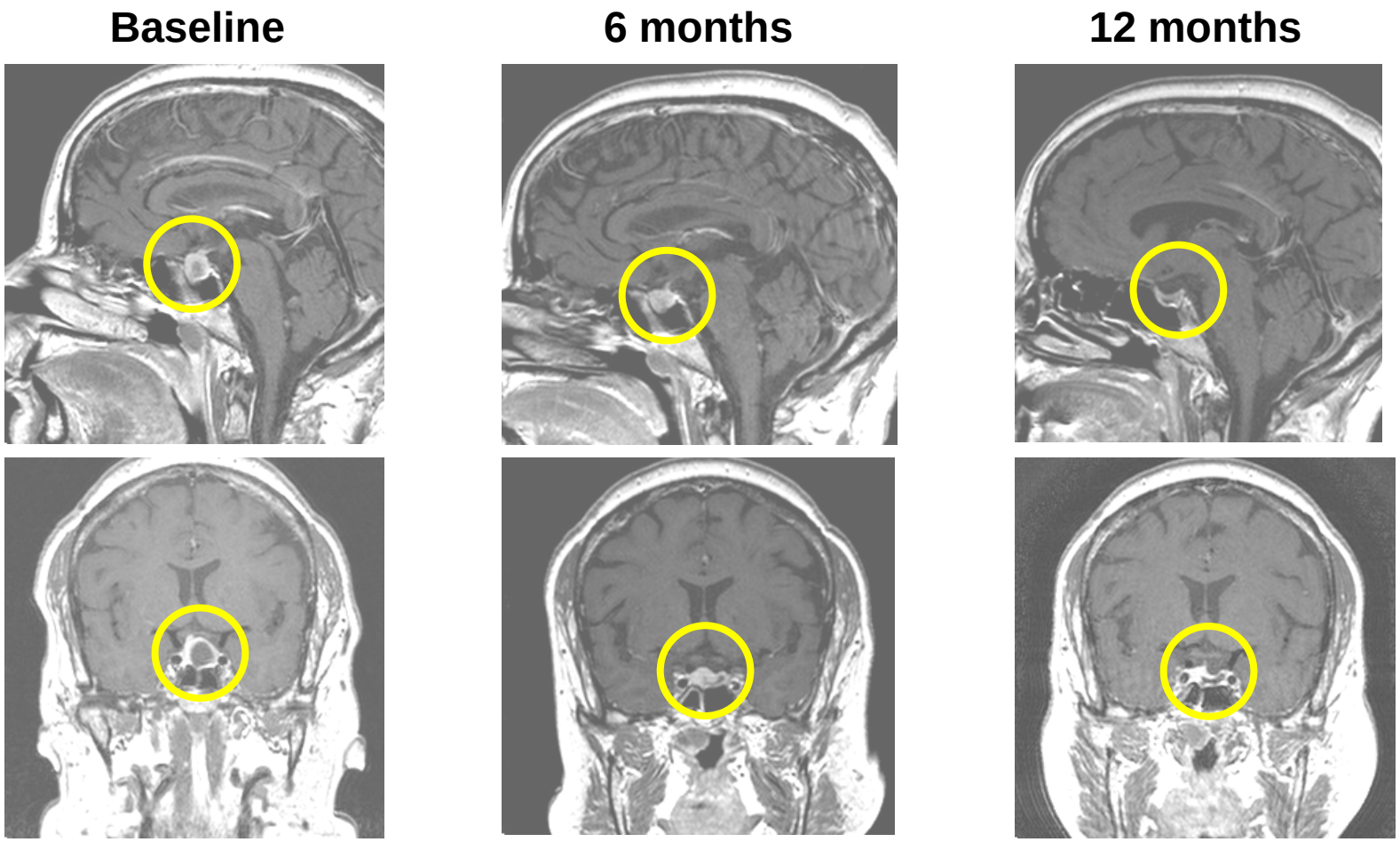
- At 6 months, 34% of patients on 600 µg and 41% of patients on 900 µg were controlled or partially controlled
- ACTH and UFC reduction was rapid and sustained
- Within 1 to 2 months, patients with less than 50% UFC reduction were evident



Colao A, et al. *N Engl J Med*. 2012;366(10):914-924.

Pasireotide Decreases Tumor Size

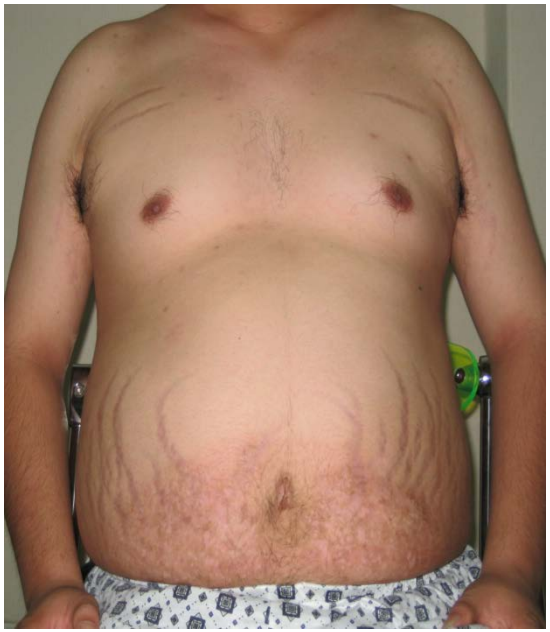
- 44% reduction in tumor volume at 12 months



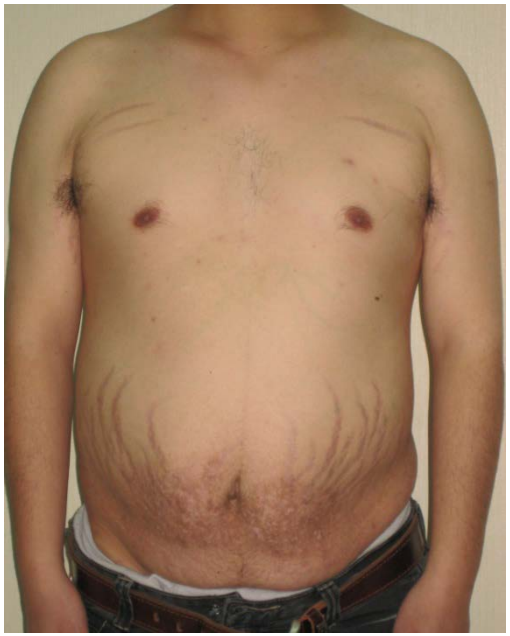
Shimon I, et al. *Pituitary*. 2012 Aug 24. [Epub ahead of print].

Pasireotide Improves Physical Features of Cushing's Disease

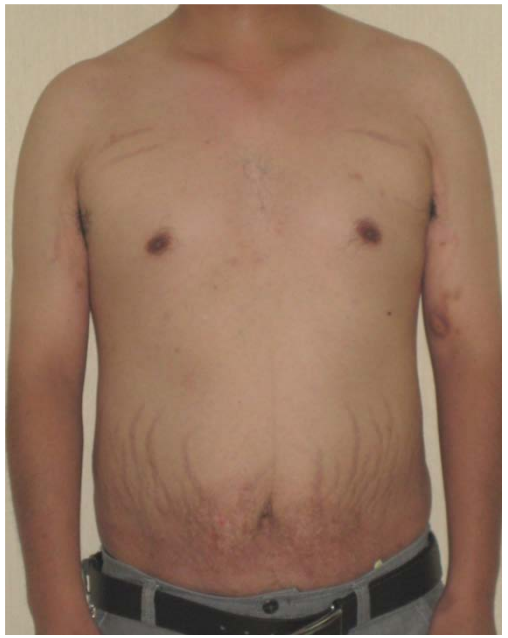
Baseline



Month 6



Month 12



Risk:Benefit Profile for Pasireotide in Cushing's Disease

Risks

- Safety profile similar to other somatostatin analogues, except hyperglycemia
- Hyperglycemia is common and should be managed promptly
- Abnormal LFTs can be identified with monitoring and are reversible
- Hypocortisolism: uncommon, readily addressed

Benefits

- Pituitary-targeted therapy
- Addresses underlying disease mechanism
- Rapid and sustained UFC reduction
- Leads to clinical improvement
- Non-responders readily detectable
- Reduces tumor volume in some patients

Clinical Perspective

- Unmet need for a safe pituitary-targeted medical therapy
  - Normalizes ACTH and cortisol levels
  - Controls tumor growth
  - Improves signs and symptoms, and HRQoL
  - Reverses comorbidities and improves survival
- Pasireotide offers new hope for Cushing's disease patients by meeting many of these stringent criteria

Supportive Slides

Reasons for Consent Withdrawal

Study B2305

- 24 patients
  - 4 related to adverse events
  - 3 unsatisfied with efficacy
  - 1 both AE related and unsatisfied with efficacy
  - 3 due to non-compliance
  - 6 wanted to have alternative therapy
  - 7 no specified reason

CTC Grading for Glycemia-related AEs

HYPERGLYCEMIA				
Blood glucose unit	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
mg/dL	> ULN–160	> 160–250	> 250–500	> 500
mmol/L	> ULN–8.9	> 8.9–13.9	>13.9–27.8	> 27.8 or acidosis

HYPOGLYCEMIA				
Blood glucose unit	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
mg/dL	< LLN -55	< 55-40	< 40-30	< 30
mmol/L	< LLN-3.0	< 3.0-2.2	< 2.2-1.7	< 1.7

DIABETES			
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Asymptomatic, intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g. ketoacidosis, hyperosmolar non-ketotic coma)

CTC, Common Terminology Criteria for Adverse Events v3.0; FPG, fasting plasma glucose; ULN, upper limit of normal.

Fasting Glucose—Newly Occurring or Worsening Abnormalities by CTC Grade

Study B2305

	Worsening from baseline to:	600 µg n = 82			900 µg n = 80			Overall N = 162		
		Total	n	(%)	Total	n	(%)	Total	n	(%)
Fasting glucose (hyper)	Grade 1	71	20	28.2	75	18	24.0	146	38	26.0
	Grade 2	74	18	24.3	76	18	23.7	150	36	24.0
	Grade 3	77	16	20.8	78	20	25.6	155	36	23.2
	Grade 4	77	0	0	78	0	0	155	0	0
Fasting glucose (hypo)	Grade 1	77	11	14.3	78	7	9.0	155	18	11.6
	Grade 2	77	3	3.9	78	3	3.8	155	6	3.9
	Grade 3	77	0	0	78	0	0	155	0	0
	Grade 4	77	0	0	78	0	0	155	0	0

Patients are counted for the worst grade only.

Patient Baseline Characteristics and CV Risk Factors

Study B2305

	600 µg n = 82		900 µg n = 80	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Age (years)	82	40.5 (12.97)	80	39.9 (10.77)
Blood pressure (mmHg)				
Systolic	82	132.0 (18.70)	80	135.0 (20.17)
Diastolic	82	85.7 (12.90)	80	87.0 (12.33)
Weight (kg)	82	81.9 (22.43)	80	81.3 (20.64)
Waist circumference (cm)	79	103.3 (18.32)	79	102.8 (17.73)
BMI (kg/m^2)	82	30.4 (7.01)	80	30.2 (7.07)
Total cholesterol (mmol/L)	82	5.9 (1.29)	80	5.7 (1.35)
HbA1c (%)	78	5.83 (0.78)	76	5.76 (0.79)

CV risk factors	**600 µg n = 82 n (%)**	**900 µg n = 80 n (%)**
Hypertension[a]	63 (76.8)	63 (78.8)
Dyslipidemia[b]	77 (93.9)	75 (93.8)
Obesity BMI ≥ 30 kg/m^2	36 (43.9)	36 (45.0)
Diabetes[c]	28 (34.1)	27 (33.8)

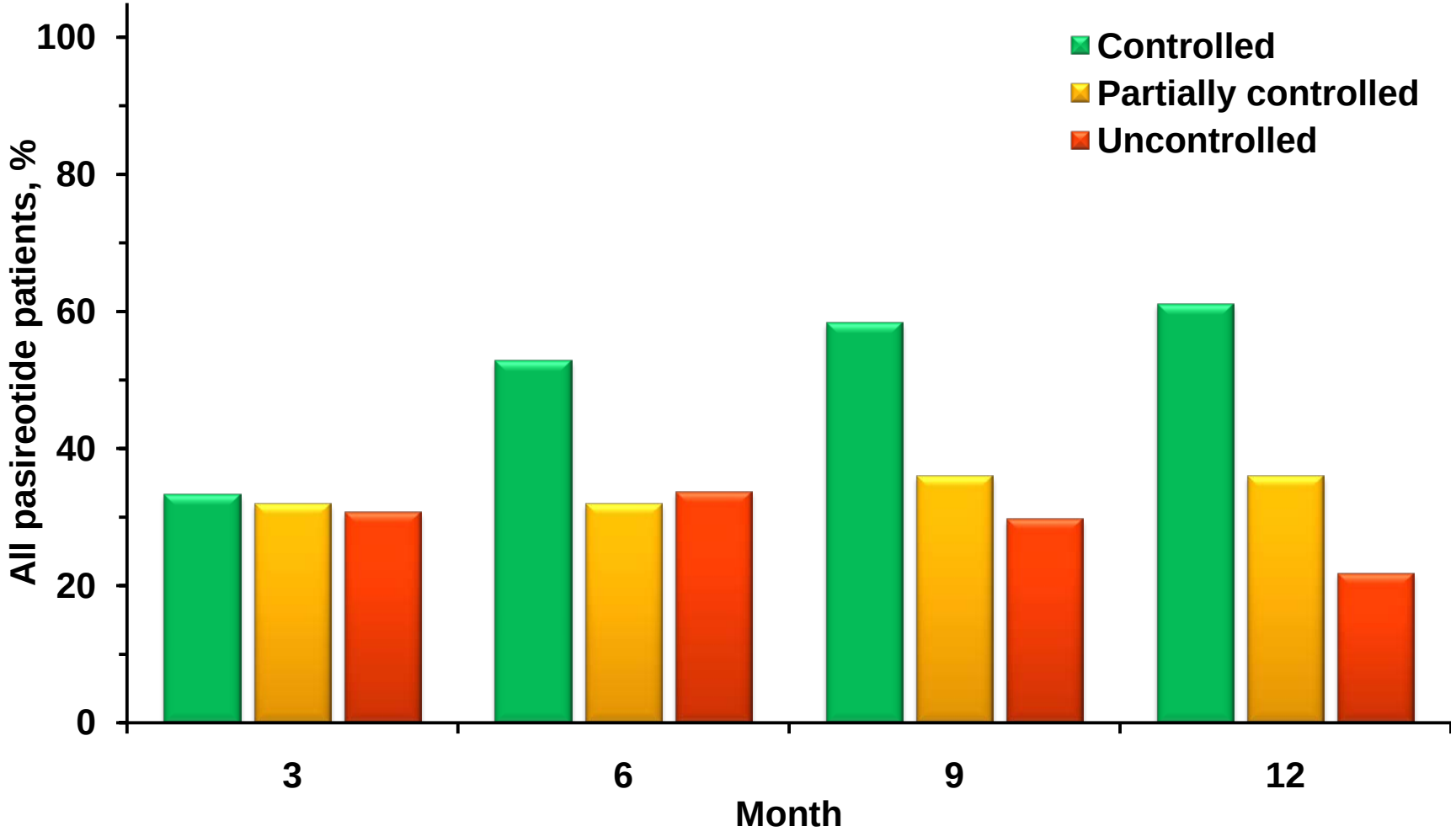
[a] Baseline hypertension = Patients with at least one of following: history of anti-hypertensive meds; medical history of hypertension; baseline sitting SBP > 130; baseline sitting DBP > 90

[b] Baseline dyslipidemia = Patients with at least one of following: history of lipid lowering meds; medical history of dyslipidemia; at baseline a TC ≥ 200 mg/dL (5.2 mmol/L), TG > 150 mg/dL (1.7 mmol/L), HDL-C < 40 mg/dL (1.0 mmol/L) in male patients or < 50 mg/dL (1.3 mmol/L) in female patients or LDL- C >100 mg/dL (2.6 mmol/L)

[c] Diabetic: Patients taking anti-diabetic medication or prior history of diabetes mellitus or HbA1c ≥ 6.5% or FPG ≥ 126 mg/dL.

Patients Achieving ≥ 5% Weight Reduction From Baseline by UFC Control Status

Study B2305—Full Analysis Set



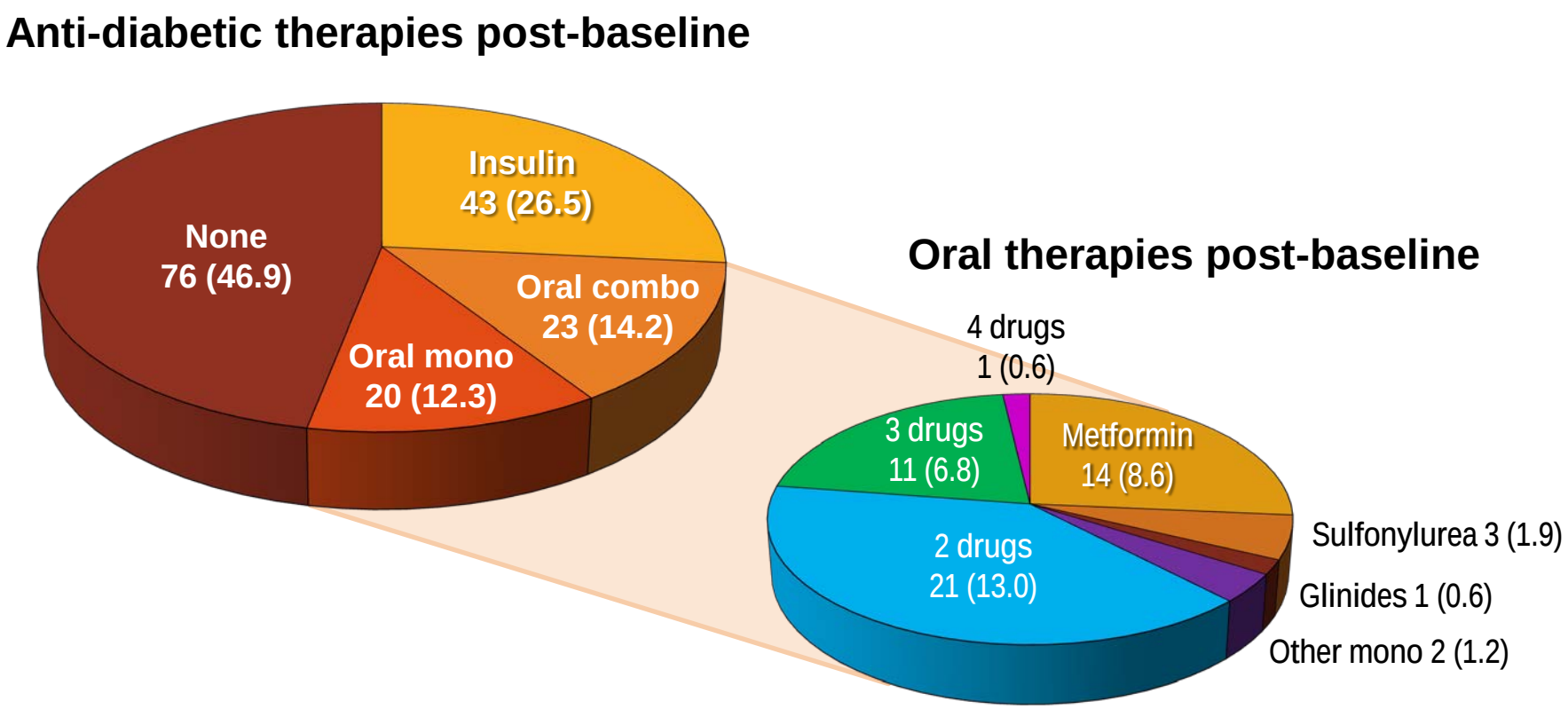
Free T4 and TSH - Changes Over Time

Study B2305

Timepoint	Mean Free T4, (11.5-22.7 pmol/L)	Mean TSH, (0.35-5.50 mIU/L)
Baseline	14.6	1.0
Month 1	14.3	1.4
Month 3	14.4	1.5
Month 6	14.6	1.5
Month 12	14.5	1.4
Mean change from baseline at Month 12	0.1	0.5

Number of Patients (%) With Specific Anti-Diabetic Therapies Post-Baseline

Study B2305



18 patients used DPP-4 inhibitor-containing regimen (2 or more drugs) in study; GLP analogs were not used.
Dosage of anti-diabetic medications was not collected during the study.

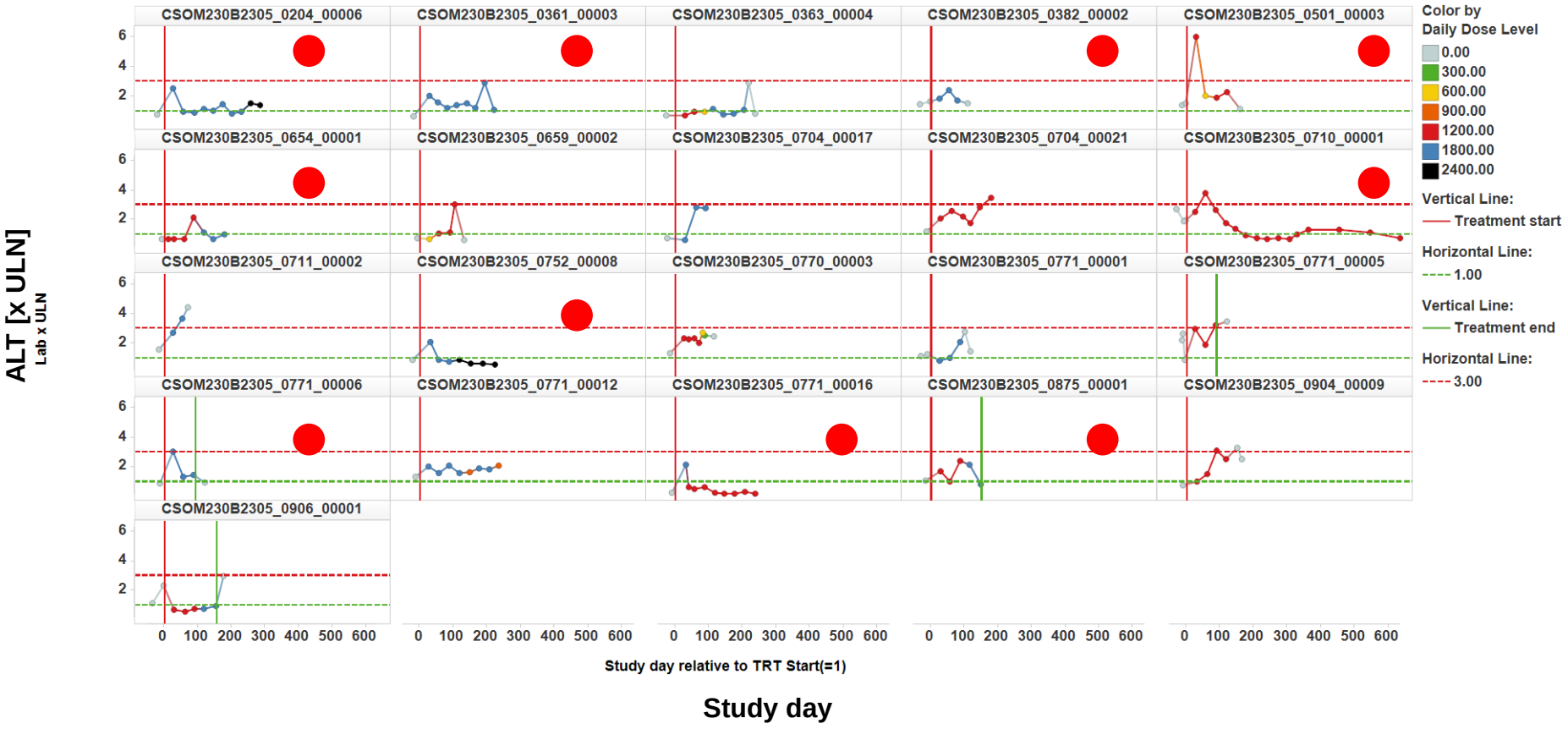
Recommended Glycemic Interventions

Study B2219

Glycemic values		Treatment recommendation
FPG result is > 130 mg/dL but ≤ 180 mg/dL HbA1c result is ≥ 7.0% but ≤ 8.0%	*or…*	DPP-IV inhibitor or a fixed-dose combination of a DPP-IV inhibitor + metformin
FPG result is > 180 mg/dL but ≤ 210 mg/dL HbA1c result is ≥ 8.0% but ≤ 9.0%	*or…*	GLP-1 analogue/mimetic or concomitant treatment of GLP-1 analogue/mimetic + metformin
FPG result is > 210 mg/dL HbA1c result is > 9.0%	*or…*	Insulin therapy or insulin therapy + DPP-IV inhibitor ± metformin

Adaptation to Pasireotide-associated Liver Effects

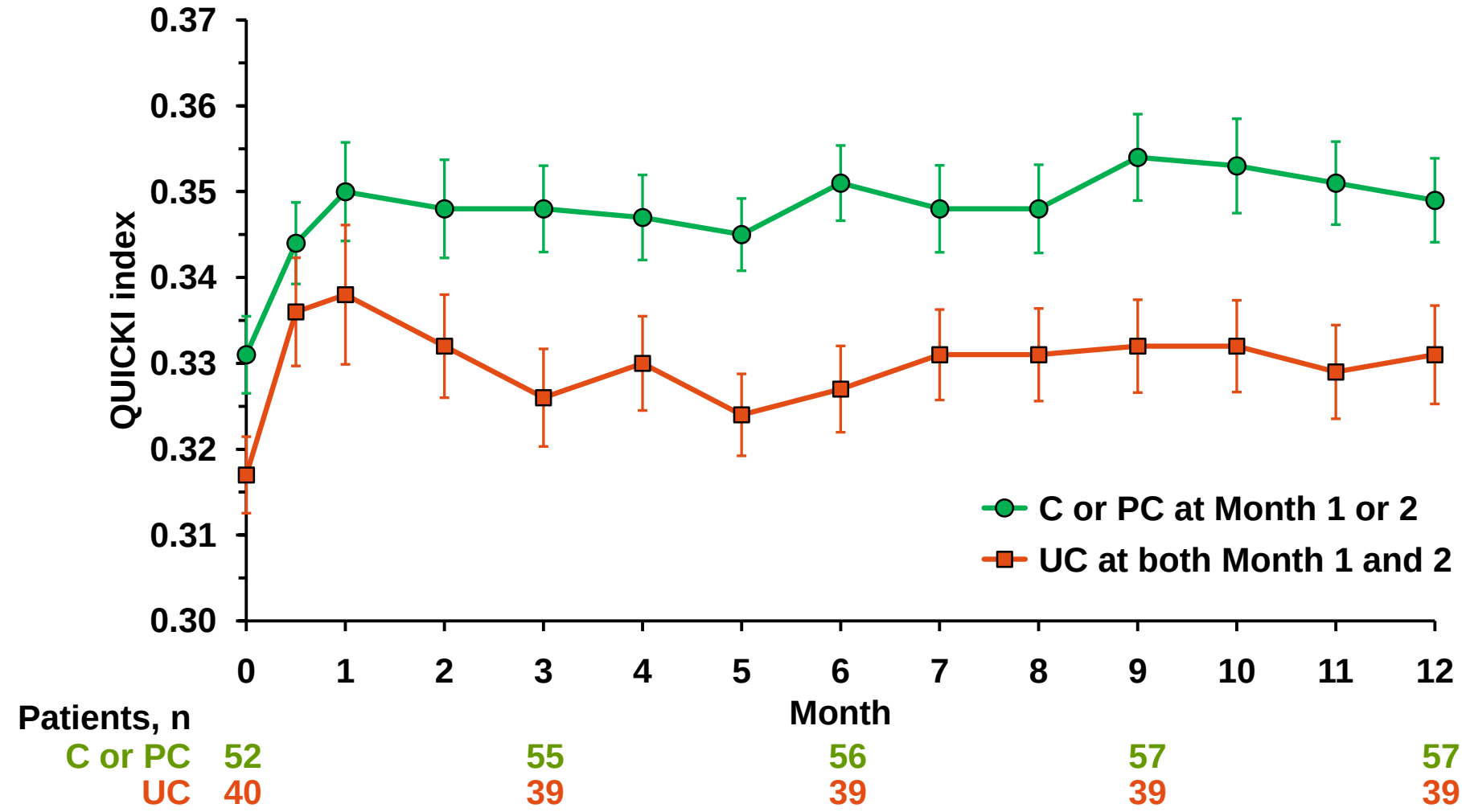
*Study B2305, all patients with **ALT ≥ 2 × ULN***



- Most patients adapt to pasireotide-associated liver effects
- Often, there are only single time points with potentially relevant ALT elevations

Insulin Sensitivity (QUICKI Index) up to Month 12 (with LOCF) by UFC Control Status at Month 1 and 2[a]

Study B2305



[a] Excluding patients who received insulin or sulfonylureas at any time post-baseline.

Acute Idiosyncratic Hepatocellular Injury

Patient #1234, 80 year old Caucasian Male, Drug X

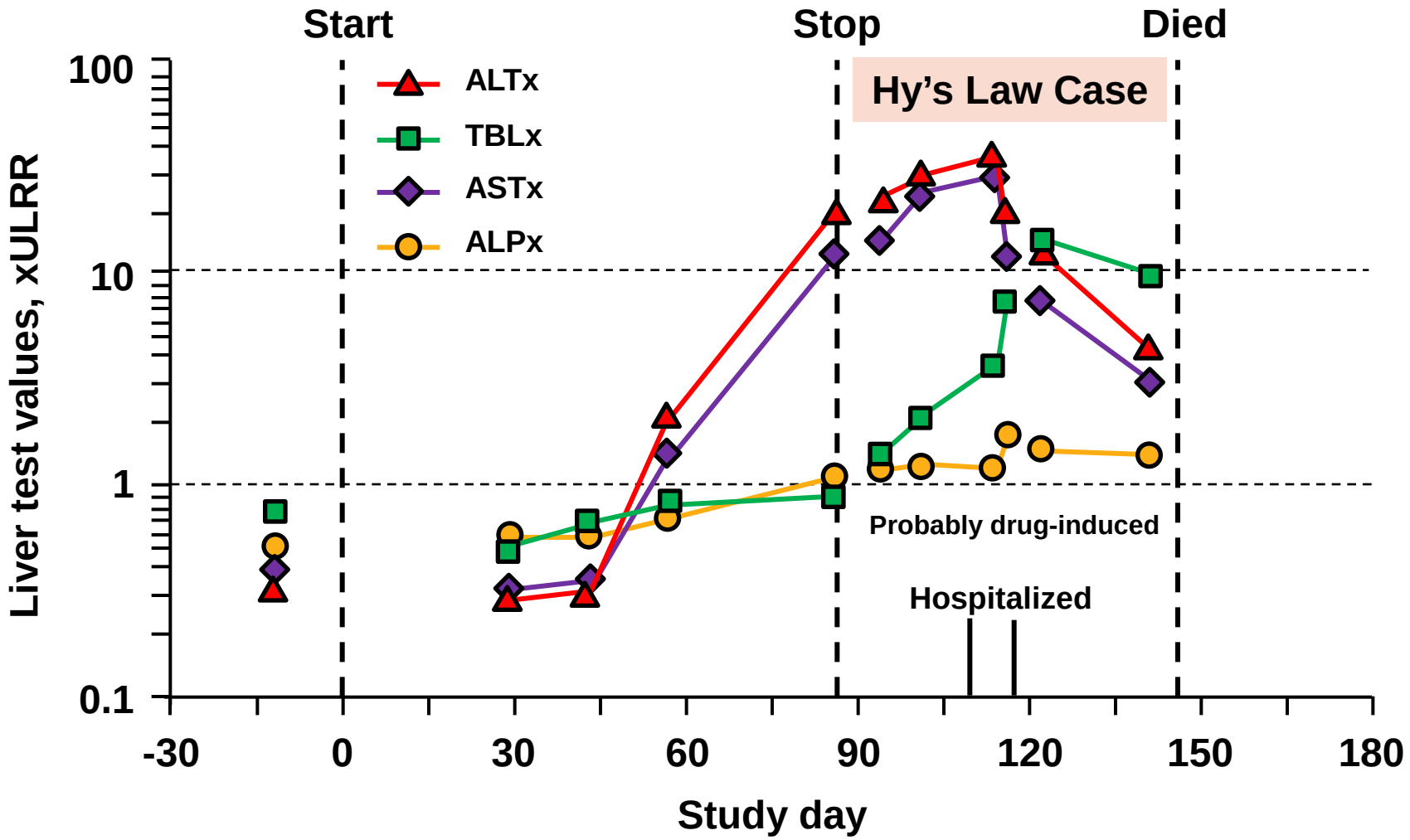
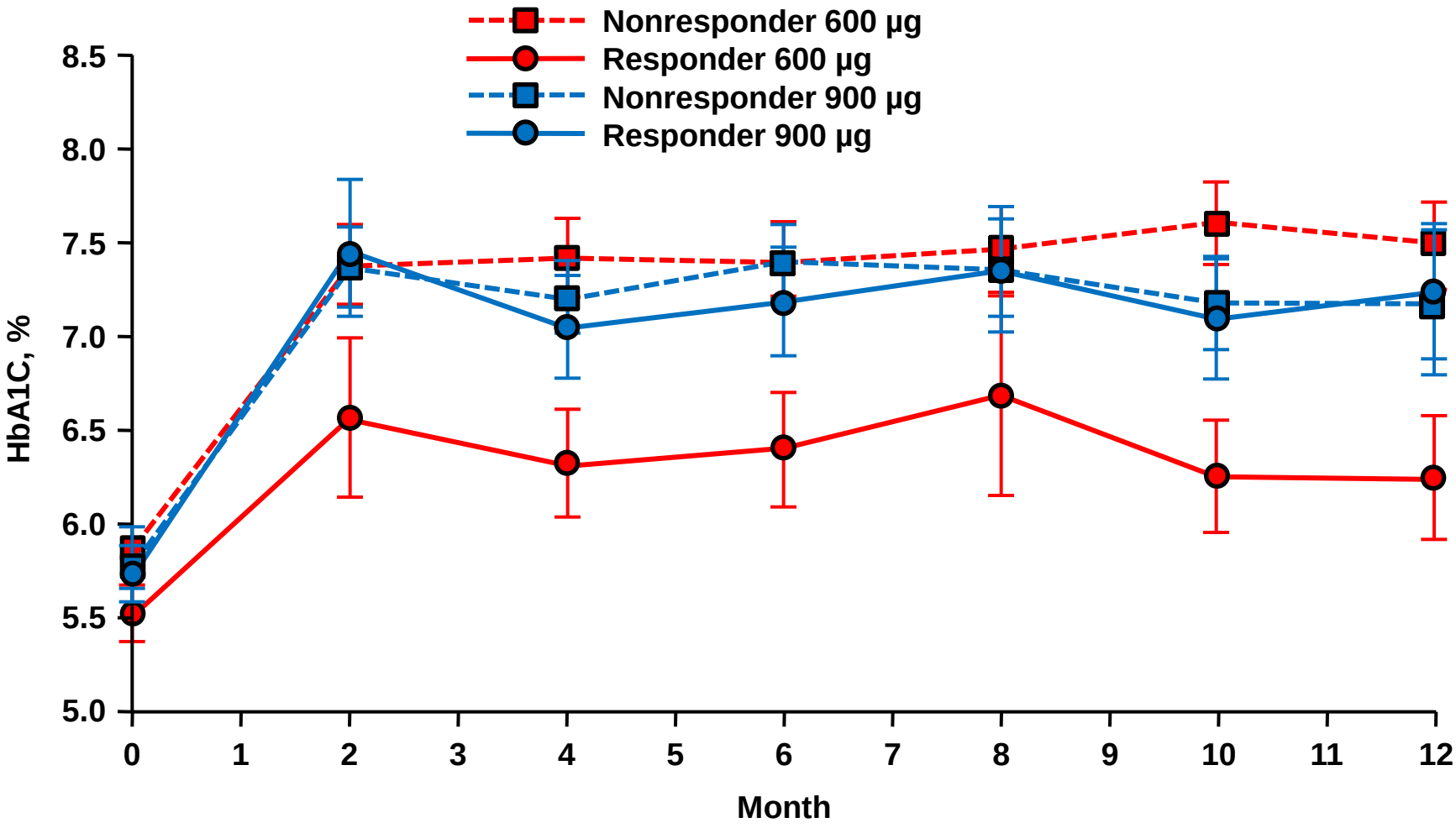


Figure courtesy of John Senior.

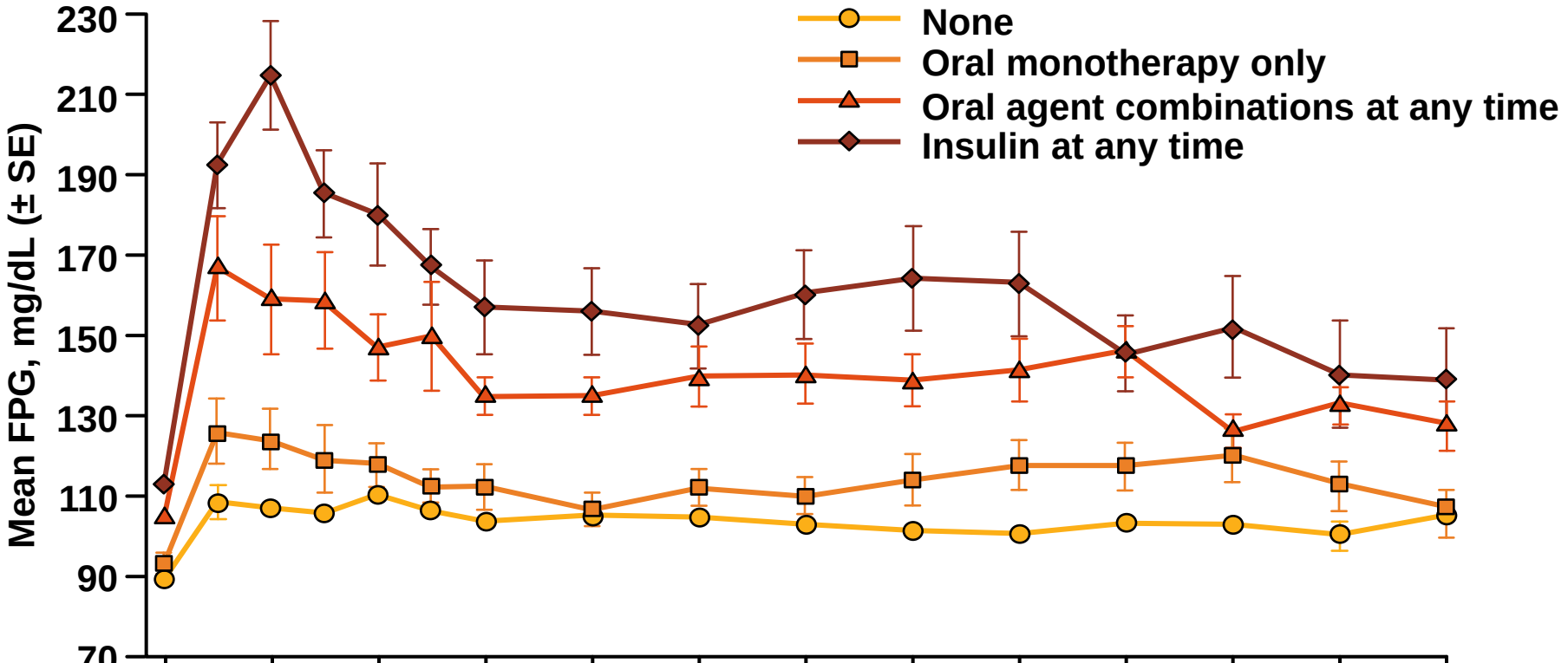
Mean (±SE) HbA1c Over Time by Responder Status

Study B2305



Mean FPG From Baseline to Month 12 by Post-baseline Anti-diabetic Therapy

Study B2305



Patients, n													
Insulin	43	40	38	36	35	33	32	27	24	23	22	21	20
Oral combo	22	22	21	20	20	20	19	19	18	17	16	15	13
Oral mono	20	20	18	17	16	16	15	14	14	14	14	14	13
None	73	66	60	62	58	50	46	43	41	40	36	34	31

AEs ≥ 5% Regardless of Study Drug Relationship

Study B2124

Primary system organ class Preferred term	Patients, n (%) Pasireotide 600 µg sc bid + Metformin 500 mg IR po bid n = 18	+ Nateglinide 60 mg po tid n = 18	+ Vildagliptin 50 mg po bid n = 18	+ Liraglutide 0.6 mg sc qd n = 18	Pasireotide 600 µg sc bid n = 18	All subjects N = 90
Any primary system organ class	18 (100.0)	18 (100.0)	18 (100.0)	18 (100.0)	18 (100.0)	90 (100.0)
Gastrointestinal disorders	17 (94.4)	18 (100.0)	17 (94.4)	18 (100.0)	16 (88.9)	86 (95.6)
Diarrhea	14 (77.8)	13 (72.2)	12 (66.7)	12 (66.7)	14 (77.8)	65 (72.2)
Nausea	11 (61.1)	15 (83.3)	7 (38.9)	13 (72.2)	8 (44.4)	54 (60.0)
Abdominal pain	8 (44.4)	13 (72.2)	5 (27.8)	9 (50.0)	6 (33.3)	41 (45.6)
Flatulence	5 (27.8)	8 (44.4)	7 (38.9)	7 (38.9)	8 (44.4)	35 (38.9)
Vomiting	1 (5.6)	3 (16.7)	4 (22.2)	5 (27.8)	1 (5.6)	14 (15.6)
Abdominal distension	2 (11.1)	1 (5.6)	4 (22.2)	3 (16.7)	1 (5.6)	11 (12.2)
Feces discolored	1 (5.6)	1 (5.6)	2 (11.1)	2 (11.1)	2 (11.1)	8 (8.9)
Abdominal discomfort	1 (5.6)	2 (11.1)	0	3 (16.7)	1 (5.6)	7 (7.8)
Eructation	1 (5.6)	1 (5.6)	1 (5.6)	0	2 (11.1)	5 (5.6)
General disorders and administration site conditions	18 (100.0)	18 (100.0)	18 (100.0)	18 (100.0)	18 (100.0)	90 (100.0)
Infections and infestations	1 (5.6)	1 (5.6)	1 (5.6)	3 (16.7)	0	6 (6.7)
Metabolism and nutrition disorders	6 (33.3)	13 (72.2)	2 (11.1)	7 (38.9)	2 (11.1)	30 (33.3)
Nervous system disorders	6 (33.3)	10 (55.6)	4 (22.2)	7 (38.9)	6 (33.3)	33 (36.7)
Skin and subcutaneous tissue disorders	1 (5.6)	3 (16.7)	0	4 (22.2)	1 (5.6)	9 (10.0)

Most Common Adverse Events of Suspected Drug Relationship (Core and Extension up to 19 Months)

Study C2305—Acromegaly (Pasireotide LAR vs Octreotide LAR)

Most common AEs in >10% of patients (PT)	Patients, n (%)	
	Pasireotide LAR N = 178	Octreotide LAR N = 180
Diarrhea	59 (33.1)	73 (40.6)
Cholelithiasis	50 (28.1)	66 (36.7)
Hyperglycemia	50 (28.1)	13 (7.2)
Abdominal pain	23 (12.9)	32 (17.8)
Alopecia	28 (15.7)	26 (14.4)
Diabetes mellitus	36 (20.2)	7 (3.9)
AEs of special interest (grouped by term)		
Hyperglycemia-related	104 (58.4)	33 (18.3)
Gallbladder and biliary-related	62 (34.8)	73 (40.6)
Diarrhea-related	59 (33.1)	73 (40.6)
Nausea-related	18 (10.1)	29 (16.1)
Pancreatitis-related	20 (11.2)	23 (12.8)
Bradycardia-related	20 (11.2)	21 (11.7)

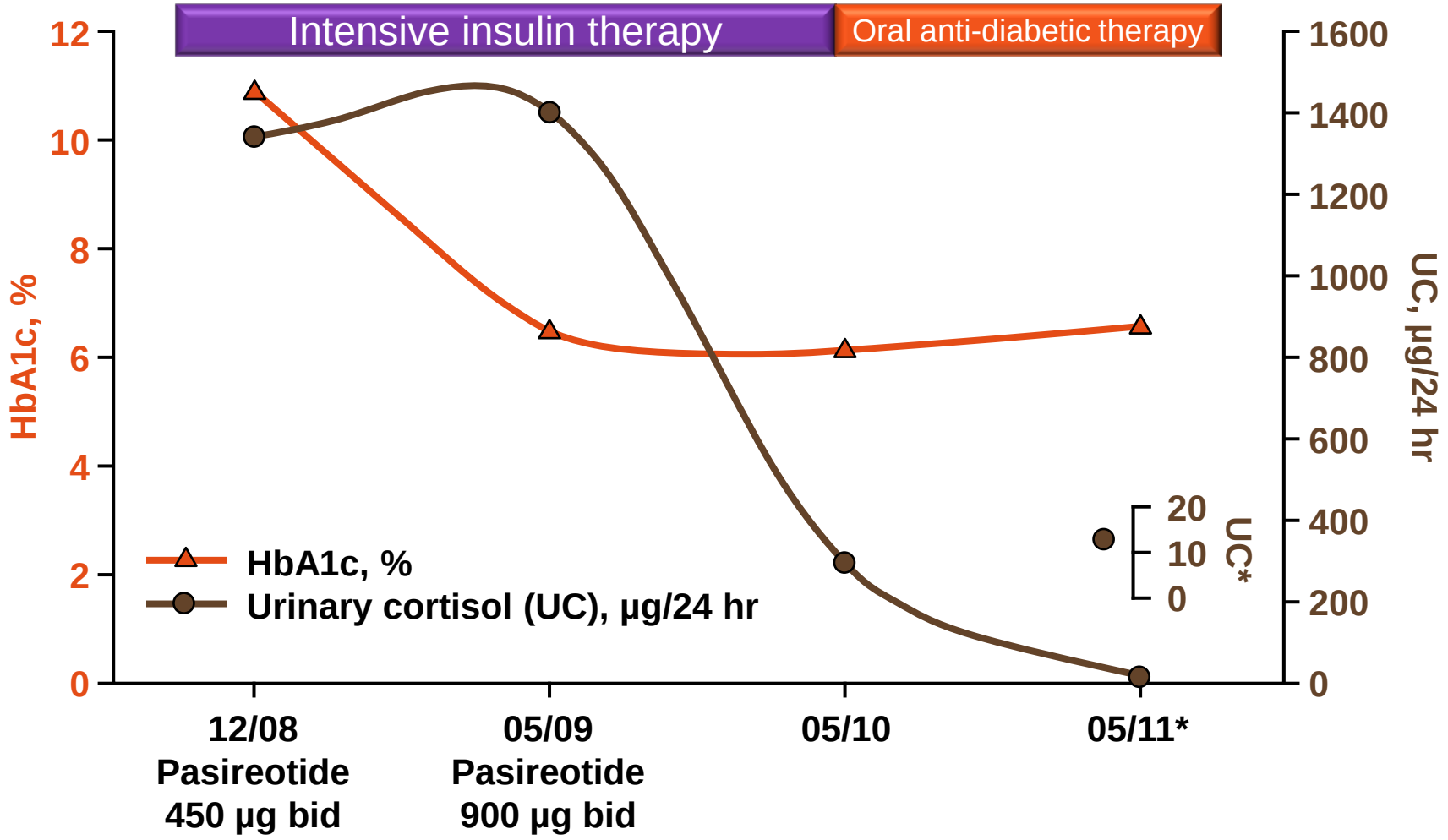
[a] **Most AEs were mild to moderate**

Case Report: Benefit of Pasireotide With Intensive Glycemic Control

- Female, age 63 years
  - Surgical resection of the tumor was not recommended
  - Starting dose: Pasireotide 450 µg bid
    - Progressively increased to 900 µg bid
- Poorly controlled diabetes at baseline (HbA1c > 10%)
  - Receiving intensive insulin therapy prior to and during pasireotide treatment
  - Insulin therapy was adjusted on a daily basis

Fiorentino C, et al. *J Endocrinol Invest*. 2011;34(9):731-732.

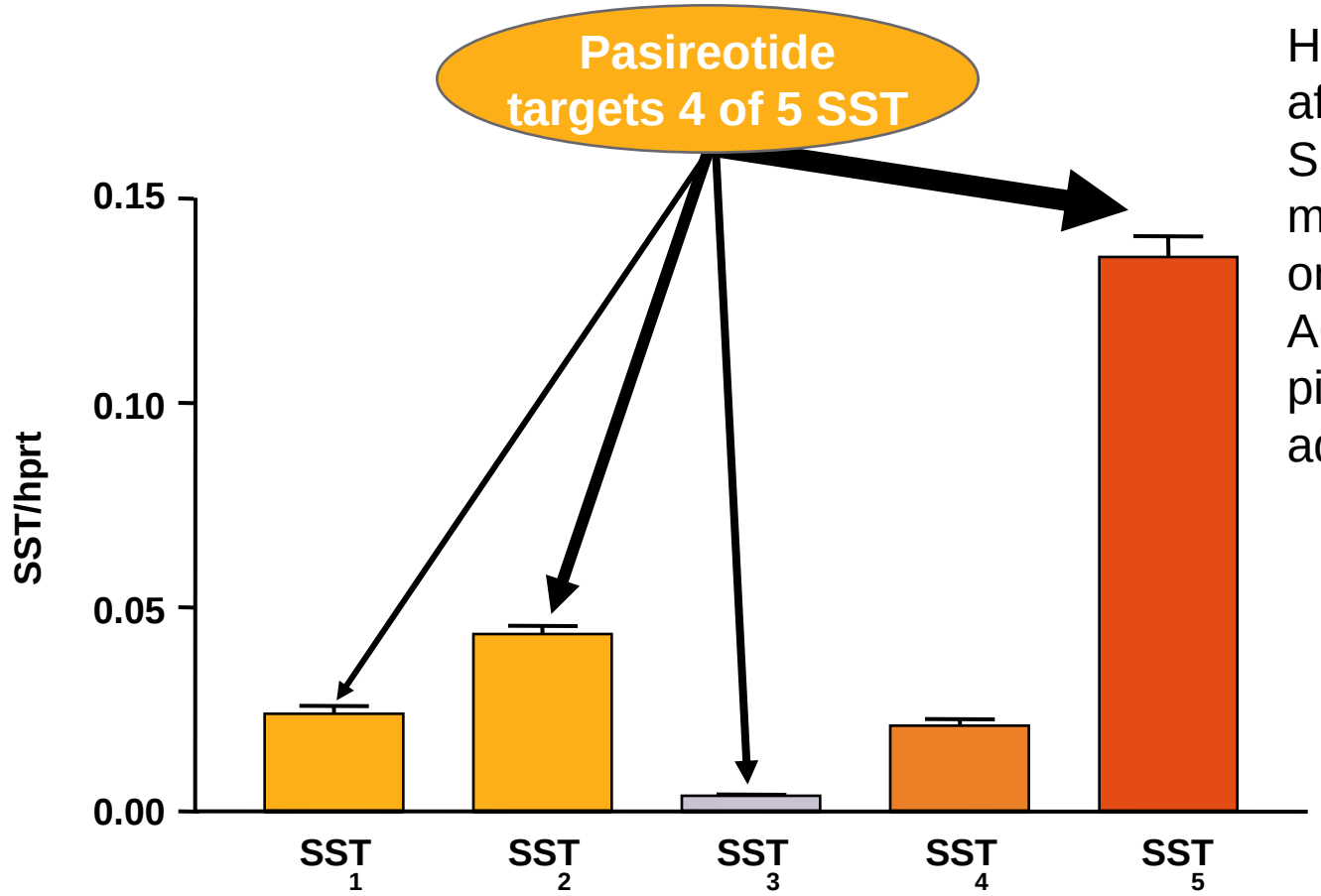
Changes in HbA1c and Urinary Cortisol Related to Therapy



OHA = oral hypoglycemic agents.

Fiorentino C, et al. *J Endocrinol Invest*. 2011;34(9):731-732.

Somatostatin Receptor Subtype Expression in Corticotroph Adenomas (N = 30)

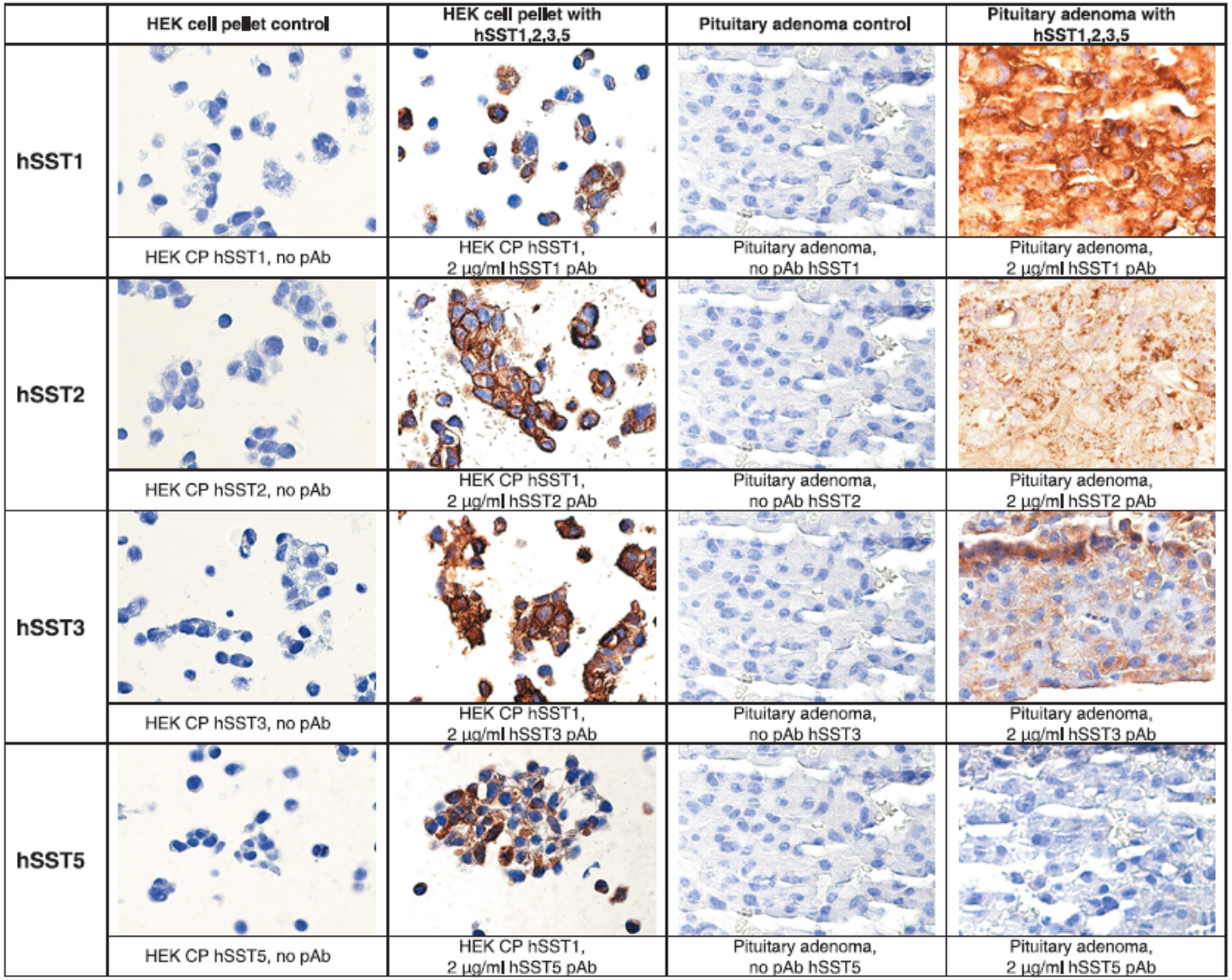


Highest affinity for SST_5, receptor most prevalent on ACTH-secreting pituitary adenomas

Pasireotide inhibits ACTH production in corticotroph adenomas *in vitro*

LJ Hofland et al. Eur J Endocrinol 2005; Batista DL et al. JCEM 2006; de Bruin C et al. Rev Endocr Metab Disord 2009; Bruns C et al. Eur J Endocrinol 2002.

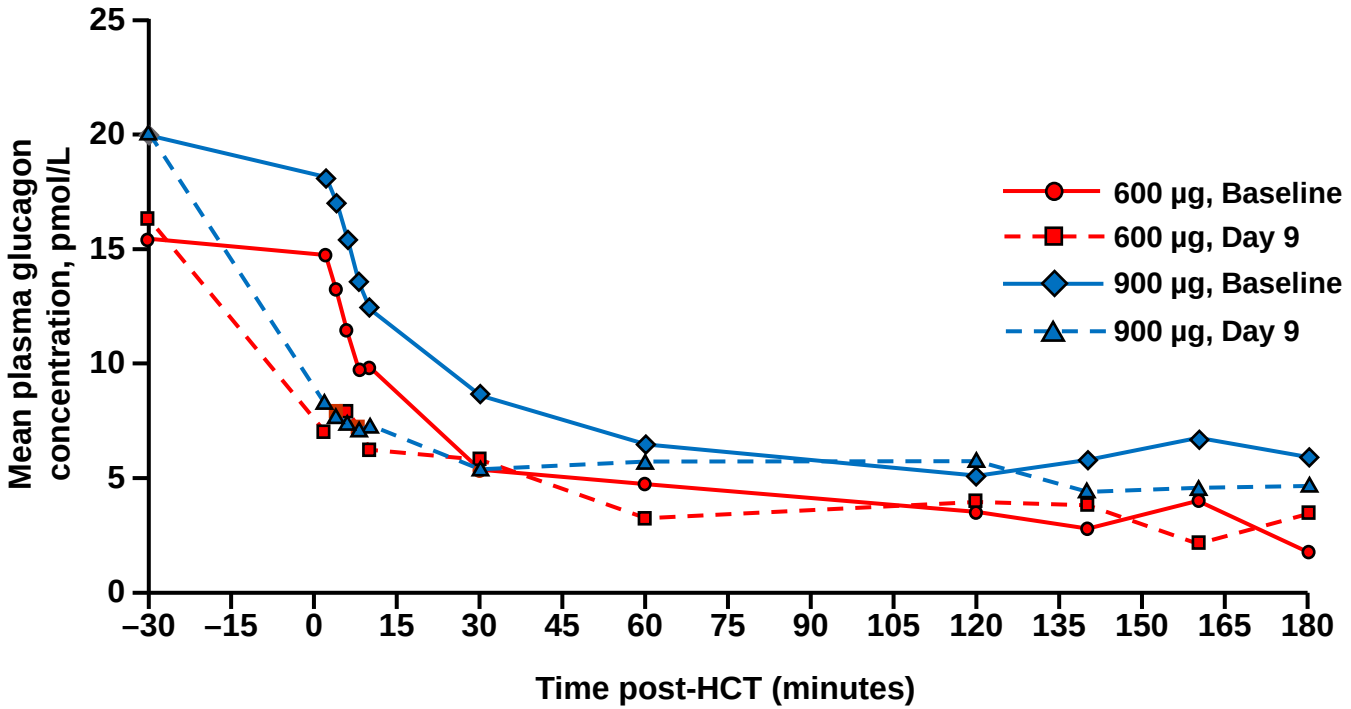
Staining of the Corticotroph Tumor



Cukier K, et al. *Clin Endocrinol (Oxf).* 2009;71(2):305-307.

Hyperglycemic Clamp Test (HCT): Glucagon

Mechanistic Study B2216



Minimal effect of pasireotide on glucagon secretion

HCT = hyperglycemic clamp test.

Association between SBP and UFC -Repeated Measures Model

- Model
  - Dependent variable: Change from baseline in SBP over time
  - Explanatory variables:
    - Baseline SBP, Baseline UFC (log scale)
    - Time-dependent variable: Post-baseline UFC (log scale) over time

- Results
  - Effect of time-dependent UFC on SBP : p-value <0.0001
  - 50% reduction in UFC reduces SBP by 1.90 mm Hg

Association between DBP and UFC -Repeated Measures Model

- Model
  - Dependent variable: Change from baseline in DBP over time
  - Explanatory variables:
    - Baseline DBP, Baseline UFC (log scale)
    - Time-dependent variable: Post-baseline UFC (log scale) over time

- Results
  - Effect of time-dependent UFC on DBP: p-value <0.0424
  - 50% reduction in UFC reduces DBP by 0.45 mm Hg